THE COLLECTED PAPERS

OF

JOSEPH, BARON LISTER

PUBLISHED BY
HENRY FROWDE, M.A.
OXFORD UNIVERSITY PRESS

AND

HODDER AND STOUGHTON
WARWICK SQUARE, E.C.
LONDON

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JOSEPH, BARON LISTER

MEMBER OF THE ORDER OF MERIT
FELLOW AND SOMETIME PRESIDENT OF THE ROYAL SOCIETY
KNIGHT GRAND CROSS OF THE DANISH ORDER OF THE DANEBROG
KNIGHT OF THE PRUSSIAN ORDRE POUR LE MÉRITE
ASSOCIÉ ÉTRANGER DE L'INSTITUT DE FRANCE
ETC. ETC.

IN TWO VOLUMES

VOL. I

OXFORD
AT THE CLARENDON PRESS
MDCCCCIX

OXFORD
PRINTED AT THE CLARENDON PRESS
BY HORACE HART, M.A.
PRINTER TO THE UNIVERSITY

PREFACE

When, on the 5th of April, 1907, Lord Lister attained his eightieth birthday, he was the recipient of many congratulations, not only from his fellow countrymen, but from representatives of medicine and surgery throughout the world, and a unanimous desire was then expressed that some permanent memorial should be instituted of so happy an occasion, and of a life so rich in benefits to mankind.

No memorial seemed more appropriate than a collected edition of his scientific papers, scattered through many different periodical publications, inasmuch as in them are recorded the steps by which the great revolution in surgery with which his name will be imperishably associated was brought about, and by their perusal succeeding generations may learn at first hand the great principle on which that revolution was based. The proposal, it was ascertained, commended itself to Lord Lister, and the Committee which has prepared these volumes for the press has had the inestimable advantage of his guidance and advice.

The two volumes contain all the papers and addresses which he himself considers to possess permanent interest and importance ; the omissions in fact are few in number, and consist almost solely of addresses on certain official occasions dealing with matters of ephemeral or merely local interest. The papers have been classified under four general heads, according as they deal with Physiology, Pathology and Bacteriology, the Antiseptic System, or General Surgery, while various general addresses and lectures are gathered together in a fifth part. In arranging the several papers in each Part chronological order has generally been followed.

The Committee has thought it well to preface the text of the papers and addresses themselves by a brief introduction giving some account of the state of surgery at the date when Lord Lister began his work, indicating the growth of the principle by which he was guided, and tracing the early stages of its application to practical surgery. Without some such preliminary statement, those unacquainted with the position of surgery, and the conditions prevalent in surgical wards in the middle of the nineteenth century, may fail adequately to understand the difficulty and complexity of the problem as it presented itself to him, and the brilliancy of the long chain of reasoning and experiment by which he was led to its triumphant solution.

NOTE

These volumes were prepared for the press by a Committee consisting of:

Sir Hector C. Cameron.
Sir W. Watson Cheyne, Bt., C.B., F.R.S.
Rickman J. Godlee, M.S.
C. J. Martin, M.D., F.R.S.
Dawson Williams, M.D., F.R.C.P.

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CHRONOLOGICAL NOTE

Born April 5, 1827.

Graduated B.A. 1847, M.B. 1852, University of London.

Edinburgh: House Surgeon, 1854; Extra-Mural Lecturer, 1855, and Assistant Surgeon, Royal Infirmary, 1856.

Glasgow: Professor of Surgery, 1860–9.

Edinburgh: Professor of Clinical Surgery, 1869–77.

London: King's College, Professor of Clinical Surgery, 1877–93.

INTRODUCTION

It is not proposed to enter into any biographical details in the following notes, which are merely intended to indicate the sequence of events in the course of Lord Lister's work, and thus to enable the reader to follow the development of his great discovery. His work was carried out at different periods and under the varying circumstances of different hospitals and clinical schools.

The first of these periods was one of preparation, ending in his graduation in medicine at the University of London in 1852. Among the men whose influence during this period was of the greatest importance in determining his future line of thought and work were his father, Joseph Jackson Lister, William Sharpey, Professor of Physiology, and Thomas Graham, Professor of Chemistry in University College.

Joseph Jackson Lister was a merchant in the City of London who devoted his leisure to scientific pursuits, and especially to the perfecting of the microscope, and his name will always be remembered as the first to solve the problem of the production of achromatic lenses. He was a man of extreme accuracy of thought, a most methodical worker, a good classical scholar, and skilful with brush and pencil. His influence on his son's character and career was very great. This has been acknowledged with gratitude by Lord Lister himself, not only in the obituary of his father, reprinted in the second of these volumes, but also on many other occasions.

During his career at University College, Lister came specially under the influence of Sharpey, and under his guidance early applied himself to the study of various physiological problems. Papers describing the results of three important researches made by him at this period are reproduced in this volume. They relate to the contractile tissue of the iris, to the muscular tissue of the skin, and to the flow of lacteal fluid in the mesentery of the mouse respectively. His keen interest, too, in the study of chemistry under Graham had an abiding effect, for it equipped his mind with a sound knowledge of the principles and methods of chemical science, which greatly aided him in many ways in his future researches, not least in devising various forms of antiseptic dressings, a task which entailed great labour and patience in the conduct of a long series of experiments extending over many years.

The second of the periods referred to was that of his first residence in Edinburgh (1852–60). After completing his course at University College, and his time of residence in University College Hospital as House Physician and House Surgeon with Dr. Walsh and Mr. Erichsen respectively, he went to Edinburgh, taking an introduction from Dr. Sharpey to James Syme, Professor of Clinical Surgery in the University, on what was intended to be only a short visit. As a matter of fact, however, this visit led to Lister's settling in Edinburgh, where he remained until he received a call to occupy the chair of surgery in the University of Glasgow. Lister appears at once to have conceived a great admiration for Syme, then at the zenith of his great powers as a clinical teacher. He respected not only Syme's skill and resource as an operator, but also the strength of his intellect and the soundness of his judgement. Syme formed a just estimate of the powers of his visitor, for on a vacancy unexpectedly occurring he appointed Lister his House Surgeon in the Edinburgh Royal Infirmary. This association resulted in a warm personal friendship, which was cemented by Lister's marriage a few years later with Syme's eldest daughter, a lady who to the end of her life was indeed her husband's helpmeet in all his scientific investigations.

Lister became successively Lecturer in Surgery in the Extra-Mural School, and Assistant Surgeon to the Royal Infirmary, and held these appointments at the time of his translation to Glasgow. The work which Lister did during this period of his life, and the direction of his thoughts, cannot be better indicated than by a glance at the writings he then published. The earliest papers were on the duration of vitality in the tissues, on the structure of involuntary muscular fibre, and on the cutaneous pigmentary system of the frog. Another group of papers dealt with the early stages of inflammation, with gangrene from arteritis, and with the coagulation of the blood both within and without the blood-vessels, while a third group was concerned with the nervous system and included observations on the functions of the visceral nerves, with special reference to the inhibitory system, on the parts of the nervous system regulating the contraction of the arteries, and on the structure of nerve-fibre. It is not difficult to perceive the interrelation of these several lines of study and investigation, and the perusal of the papers in which they are embodied affords an interesting example of acute reasoning applied to the interpretation of the results of accurate observation and experiment.

The third distinct period of Lord Lister's life was that during which he occupied the chair of Systematic Surgery in the University of Glasgow (1860 to 1869). He there found himself in charge of a large number of beds in the old Royal Infirmary, to which, serving as it did the requirements of a great manufacturing city, accidental wounds of all sorts and degrees were daily admitted. From its wards, as he has related in the papers on the effects of the antiseptic system upon the salubrity of a general hospital here republished,[1] septic diseases were seldom absent, and the mortality from wounds and after all surgical operations was enormous. At the beginning of his career in Glasgow we find him continuing his work on the coagulation of the blood, the subject to which he devoted the Croonian Lecture delivered before the Royal Society in 1863; but he published also several important contributions to practical surgery, including the introduction of a new method of excising the wrist-joint, and the preparation of articles on anaesthetics and on amputation for *Holmes's System of Surgery*.[2]

But the gravity and constant prevalence of septic diseases in his wards, and the distressing mortality which occurred in consequence thereof, often in the most promising cases, so disappointed, pained, and distressed him, that his thoughts became more and more turned to the question of the cause and prevention of these disasters. Very many methods were tried in the hope of improving the treatment of wounds and the salubrity of his wards, for he was not satisfied to accept the fatalistic view then prevalent that septic diseases of wounds were unavoidable incidents, as much acts of God as a hail in harvest, and matters, therefore, in regard to which the surgeon had no personal responsibility. It was out of this divine discontent with things as they then were that there grew up the great work of his life, the introduction of the antiseptic method of wound treatment. During the remainder of this period of his life the majority of the papers he published were concerned with this subject, and others, such as those on the methods of ligaturing blood-vessels and stitching wounds, had a direct and essential bearing upon it. While his main aim was from the first and always the prevention of sepsis in wounds, he at the same time recognised, equally from the beginning, the importance of diminishing and as far as possible neutralizing the irritation of the wound and the general toxic effects which might be produced by the chemical substances employed as antiseptics.

The fourth period in his life was that during which he occupied the chair of Clinical Surgery in the University of Edinburgh. To this he was appointed by the Crown on the resignation of Mr. Syme. He assumed its duties at the beginning of the winter session of 1869. Already in Glasgow the soundness of the principles on which he was proceeding had been thoroughly established, but the methods by which those principles were carried into practice were still cumbrous and far from perfect; during his incumbency of the Edinburgh Chair he was largely occupied in devising and testing improvements in the methods of carrying out the antiseptic principle, with the object of rendering its use in

[1] Vol. ii, pp. 123 and 156.

[2] These articles, revised at a later date, are reprinted by permission of Messrs. Longmans at p. 135 of this volume, and p. 378 of volume ii.

everyday practice simpler. The writings published during this period are, as will be seen by reference to the second volume, chiefly devoted to such matters. At the same time he carried out investigations and published papers on other allied subjects, as, for example, on the germ theory of putrefaction, and on lactic fermentation.

The last period of Lister's active life dated from 1877, when he went to London in response to an invitation from the authorities of King's College, to fill the chair of Clinical Surgery in succession to Sir William Fergusson. This period, which extends until his retirement from active surgical work in 1892, may be characterized as one in which the final details of antiseptic surgery were more or less perfected. Various fresh antiseptics were tested, especially with the view of obtaining some antiseptic dressing which, while as reliable as the carbolic gauze, might yet prove less directly irritating, and being non-volatile might be trusted for longer periods, thus avoiding the necessity for frequent change of dressings and disturbance of the wounds. During this period, his method of treatment approximated more and more to his ideal of converting open wounds, as regards their subsequent course, to the condition of subcutaneous injuries.

These preliminary remarks cannot be more appropriately brought to a close than by a reference to the unwearied help that Lady Lister afforded to her husband in the pursuit of his investigations throughout her life. Those who were admitted to the inner circle can never forget the vivid interest which she took in the details of his work, and the many closely written volumes of dictated notes in her handwriting containing full records of the experiments on which the conclusions expressed in the essays reproduced in these volumes were largely founded.

PHYSIOLOGICAL AND PATHOLOGICAL WORK

In his Huxley lecture,[1] delivered in 1900, Lord Lister has given an account of some of his early physiological researches. In it he dwelt particularly on those researches which were more intimately connected with the development of his ideas upon the nature and causation of inflammation and suppuration.

From this account it can be seen how Lister's ideas of these processes gradually matured. It wanted only the conception of infection to complete them, and this was supplied in Pasteur's discovery of the causation of putrefaction, the full significance of which Lister was thus able at once to realize.

This chapter of scientific discovery could hardly have been more pleasingly

[1] Vol. ii, p. 515.

told than by the author himself, so that it is here only necessary briefly to review Lister's principal investigations in physiology and pathology as contributions to these sciences.

It is not surprising that Lister's first investigations should have been histological. His father, Joseph Jackson Lister, who had by his optical experiments very greatly improved the compound microscope, was an accomplished microscopist and made important discoveries concerning the structure of zoophytes and acidians. At this period the theory of the microscope was being rapidly developed, and each consequent improvement in this instrument of research opened up further fields to the investigator. Kölliker had recently discovered the cellular structure of plain muscular tissue and the first investigations of Lister were concerned with the contractile tissue of the iris[1] and skin[2], and with the structure of involuntary muscular fibre generally.[3] The observations and conclusions of Kölliker were at this time by no means universally accepted, but Lister's work not only vindicated their accuracy, but cleared away many apparent discrepancies between the observations of different observers. He also made a number of new observations upon the structure and distribution of smooth muscle fibres. These three papers were illustrated by excellent camera-lucida drawings made by Lister himself, which are reproduced in the present volume.

At the time when the last of these papers was written Lister had already commenced an inquiry into the process of inflammation,[4] a subject to which he seems to have been irresistibly attracted from the first; around it, henceforth, almost all his researches centred, although he often made wide excursions to investigate physiological problems encountered in efforts to interpret some one or other of the processes concerned in inflammation.

The investigation of the nature of the process of inflammation was, for the most part, made by direct observation upon the frog's web, a method which permitted the study of the phenomena from the beginning. Therein lay its great fertility. His observations were, however, carefully controlled by observations made upon the higher animals and man. The phenomena of stasis, and the vascular reaction, immediate and subsequent, following the application of irritants of all classes were for the first time accurately described. The former was shown to be due to the direct action of the irritant upon the blood-cells and blood-vessels, and the latter to be occasioned reflexly through the nervous system. These observations upon the early stages of inflammation were communicated to the Royal Society in 1857. They have formed the basis of all subsequent discoveries, and the conclusions drawn are as valid to-day as then.

[1] Vol. i, p. 1. [2] Vol. i, p. 9. [3] Vol. i, p. 15. [4] Vol. i, p. 209.

The vascular reaction to irritation was found by Lister, as has been said, to be indirectly produced through the medium of the central nervous system. That the calibre of the arteries was controlled by the nervous system had recently been established by Claude Bernard's discovery that section of the cervical sympathetic was followed by dilatation of the blood-vessels in the head and neck, and Waller's observation that stimulation of this nerve caused constriction in the same area. Waller and Budge also had just shown that the fibres of the cervical sympathetic, stimulation of which occasioned constriction of the vessels, emanated from the upper dorsal region of the spinal cord. On the other hand, Wharton Jones had stated that whilst division of the sciatic nerve was followed by extreme dilatation of the vessels in the frog's web, section of the roots of the sciatic within the spinal canal failed to produce this effect, whence he inferred that the constrictor fibres in the sciatic trunk came not from the cord but from the 'Sympathetic system'.

Lister, who was no doubt interested in the control of the calibre of the blood-vessels primarily on account of his observations upon the vascular reaction in inflammation, proceeded to make an investigation to ascertain which parts of the nervous system regulated the contraction of the arteries,[1] with the view of clearing up the apparent discrepancy suggested by the observations of Waller and Budge and Wharton Jones respectively.

The experiments were made upon the frog, and the size of the vessels of the web directly observed and measured by an eyepiece-micrometer. Both webs were simultaneously under observation, so that when the nervous connexions of the one side were interfered with, the other served as a control. With this simple technique he conducted a series of experiments, which even at the present time could not fail to excite admiration on account of the simple directness of their conception and the ingenuity with which they were carried out. He showed how Wharton Jones was led to a false conclusion, and established the fact that the fibres controlling the calibre of the vessels in the web of the frog issue from the spinal cord, as do those through which sensation and motion are effected in the hind limbs. He further demonstrated that the greatest focus whence those fibres emerged was at the posterior end of the cord, so that if this portion of the spinal axis were removed, intense dilatation ensued. Unless, however, the amount of cord removed was extensive, after an interval of some days the vessels recovered to some extent their former calibre, showing that the supply is not absolutely confined to any limited region. Experiments on frogs in which the whole nervous system had been destroyed, and upon amputated limbs also, led him to conclude that there must in addition be

[1] Vol. i, p. 27.

a local co-ordinating mechanism, but that this local mechanism was dominated by the central nervous system.

In the course of these investigations Lister had under frequent observation the stellate pigment-cells of the frog's skin, the concentration and diffusion of the chromatophorous particles within which produce the temporary variations in colour of the animal. The diffusion of the particles throughout the stellate cells causes the tint to darken, whereas their concentration in the body of the cell produces the opposite effect. Lister noticed that when the animal struggled, the particles moved suddenly and energetically in the direction of the body of the cell, as if acted upon by some stimulus. Convinced that he was observing a vital phenomenon of great physiological importance, he determined to investigate it.[1]

Von Wittich had found that the process was under the influence of the nervous system and that the sciatic nerve contained fibres which controlled the condition of the pigment-cells of the hind limbs. Lister confirmed these observations and further succeeded in demonstrating the mechanism of control, and showed that the adaptation of the colour of the frog to its surroundings was brought about reflexly by light entering the eye.

Lister also made observations of the first importance upon the nervous mechanism of the musculature of the gut.[2] These experiments were primarily undertaken to test Pflüger's conclusion that the splanchnic nerves contained special inhibitory fibres distributed to the muscular coats of the intestine. Lister verified Pflüger's results, but did not accept his interpretation. He came to the conclusion that both the observations of Pflüger and his own experimental results were not inconsistent with the view that the same fibres produce increased and diminished muscular activity, according to the strength of the stimulus impressed upon them. Although later work has justified the interpretation of Pflüger, the experiments devised by Lister to test this hypothesis led him to important conclusions regarding the mechanism of intestinal movements, namely, that there was an intrinsic nervous apparatus which co-ordinated the movements of successive muscular fibres in peristalsis, and that the latter could be stimulated or checked by impulses coming from other parts of the nervous system.

Another department of physiology to which Lister made considerable contributions was the causation of the coagulation of blood.[3] His attention seems to have been drawn to this subject by the coagulation of blood in an inflamed artery, and the question presented to him was, why does blood clot in contact with an inflamed vascular wall, whereas it remains fluid when surrounded by healthy endothelium?

[1] Vol. i, p. 48. [2] Vol. i, p. 87. [3] Vol. i, pp. 69, 105, 109, and 180.

At this time knowledge of physiological chemistry was but little advanced. It is only now, fifty years after Lister's work, that we are beginning to arrive at an adequate interpretation of the complicated phenomena of coagulation, and that an answer to the question with which Lister was confronted is forthcoming. At that date all that could be vouchsafed to the most patient and gifted experimenter was to remove false conceptions and accumulate a number of accurate observations to serve as guide-posts for future workers. This Lister accomplished. He showed the untenability of the then prevalent theory of Richardson that coagulation was due to the escape of ammonia when blood was shed. Both in so doing and afterwards in seeking for an explanation why blood should comport itself so differently when in healthy living vessels, and when in contact with ordinary solids, he discovered a large number of cardinal facts concerning coagulation which have been, and will in the future still be, of service to investigators in their efforts towards complete understanding of the phenomena of the clotting of blood.

SURGICAL WORK

A just conception of the value of Lister's surgical work can only be formed if the state of surgery and the conditions of surgical practice towards the middle of the last century are borne in mind. The results of surgical operations are now so generally good that it is hard to realize what they were before Lister began his reform. At that time, though they naturally varied a good deal in different hands and under different sanitary conditions, the broad facts with regard to the very unsatisfactory results of the surgical treatment of wounds and the dangers of operations were much the same in every country and in every hospital. Putrefaction of the discharges present in and escaping from the wounds occurred in almost every case, and was accompanied by more or less local inflammation. Wounds were, during their early stages, swollen and painful, and this local inflammation was constantly attended by more or less fever, which usually lasted for several days. Union by first intention was of very rare occurrence ; it was indeed impossible in large wounds, owing to the fact that the ligatures with which the vessels were tied had subsequently to be extruded by a process of granulation and suppuration ; the suppuration which necessarily occurred along the track of the ligatures usually spread to the rest of the wound. Associated with this process of separation of the ligatures was another danger, from the dread of which the surgeon's mind was never free : this was the fear that the process by which this separation was brought about might open up the lumen of the vessel, and lead to so-called secondary haemorrhage.

Still more serious than these local troubles was the frequent occurrence of general septic diseases, such as septicaemia, pyaemia, erysipelas, tetanus, or hospital gangrene. In a large proportion of the cases in which a wound of any considerable size was produced, whether by an accident or by the surgeon's knife, the patient suffered more or less severely from one or other of these surgical diseases. After major amputations, for example, the mortality was very high; the average in the practice of various surgeons at that time varied from 30 to 50 per cent. Lister collected his statistics of amputation for two years (1864 and 1866), just before he introduced the antiseptic method of treatment, and found the mortality to be 45 per cent.[1] The causes of death are not definitely stated, but almost all the deaths were due to infective diseases; for example, of six deaths following amputation of the upper extremity four were due to pyaemia and one to hospital gangrene. In his paper on excision of the wrist-joint, published in 1865, he refers to fifteen cases in which he had performed this operation, and incidentally remarks that six were attacked by hospital gangrene, while one died of pyaemia.[2]

Volkmann, in one of his earliest papers[3] on antiseptic treatment, stated that for the four years preceding the adoption of Lister's method, that is down to 1872, he had left his wounds entirely open. During the first year in which this method was carried out, the results were very favourable, and he was thoroughly convinced of its superiority over the plans which he had formerly adopted. As time went on, however, and as overcrowding of the wards became unavoidable, infective diseases of wounds increased progressively, and at last, in the summer and autumn of 1871, the deaths from pyaemia and septicaemia were so numerous that he made up his mind to close the hospital altogether for a time. Before resorting to this desperate remedy, however, he determined to try the Listerian method for a few weeks, and the result of this trial was entirely to alter the aspect of affairs.

Similar facts were published by Nussbaum of Munich, who commenced the treatment two years later than Volkmann. The hospital at Munich, a building by no means satisfactory as regards sanitary arrangements, became a hot-bed of septic infections to so great an extent that almost every case of open wound was attacked by one or other of these diseases. Pyaemia was rife, affecting nearly all cases of compound fracture, wounds of bones, and amputations. Erysipelas was constantly present. During 1872 hospital gangrene also appeared, and steadily spread in spite of all the precautions which experience dictated or ingenuity could devise; in that year 26 per cent. of all the wounds were attacked by this dreaded disease; during 1873 the proportion increased to

[1] See vol. ii, p. 129. [2] See vol. ii, p. 440 [3] *Beiträge zur Chirurgie.*

50 per cent., and it ultimately reached 80 per cent. Erysipelas, too, which in 1872 was of a comparatively mild type, became much more virulent as well as more frequent. All this occurred in spite of the use of antiseptic lotions, of the open method, and other devices. In 1878, after he had put Lister's method to the test of practice, Nussbaum published an essay entitled *Sonst und Jetzt*, in which he drew the following striking contrast between the previous state of affairs and that which followed the introduction of Listerism :

Formerly.	*Now.*
Injuries of the head, compound fractures, amputations and excisions, in fact almost all patients in whom bones were injured, were attacked by pyaemia. For example, of 17 cases of amputation 11 died from this cause. Even patients with severe whitlow died from it.	No pyaemia.
Hospital gangrene had got the upper hand to such an extent, that in spite of the open method, in spite of continuous water-baths, in spite of the use of chlorine water, or the actual cautery, finally 80 per cent. of all wounds and ulcers were attacked, large arteries being opened into.	No hospital gangrene.
Almost every wound was attacked with erysipelas.	No erysipelas.

It would be easy to produce a great cloud of witnesses to the appalling state of matters in various hospitals before the introduction of the Listerian method, but their testimony would merely be a repetition of the above statements. It is true that these untoward results were witnessed most often and in their direst form under hospital conditions of a particularly insanitary kind, and that their frequency and severity varied considerably, according to the methods of wound treatment adopted. Nevertheless these infective diseases were present everywhere, and it will readily be understood that the dread of them, never absent from the surgeon's mind, was a serious bar to progress.

Further, the operations undertaken in those days were very different from those now commonly performed. Surgical intervention was then limited more or less entirely to operations absolutely necessary for the saving of life. Operations of expediency, designed to add to the patient's comfort or to make his life more useful, were not deemed justifiable owing to the probability of the onset of some form of infection, and the consequent risk of the development of one of the severe general infections which so frequently ended in death. The major operations then performed were for the most part amputations for injury and disease, excision of joints, amputation of the breast, removal of tumours, operations on the jaw and tongue, trephining, operations for strangulated hernia, operations on the urinary organs, and certain plastic operations. Abdominal surgery, as we now understand it, did not exist, the extensive operations for malignant growths and tuberculous disease now generally practised were not performed, and the numerous exploratory operations undertaken at the present day were not even contemplated. In fact, modern surgery dates from the introduction of the Listerian methods.

The treatment of wounds as practised at different periods varied greatly, according to the views taken by different surgeons as to the causes of the septic troubles which were so prone to arise. But until Lister framed and began to test the antiseptic hypothesis, the whole subject of the diseases of wounds was in a state of chaos.

It may be interesting to mention some of the chief methods of wound treatment in vogue during the early part of the nineteenth century. At that time the air was looked on as the cause, in some way or other, of the troubles resulting from wounds, and many surgeons attempted to exclude it by putting on great masses of dressings and ointments. A reaction against this method of treatment set in, leading to the development of what was called the open method of treating wounds. In that plan the wound was left freely open, no more being done than to provide means for allowing the discharges to flow freely away, and to prevent contact of clothing. This gave results in many ways superior to those obtained from methods previously in vogue.

Another plan which also furnished good results and is still employed in suitable cases, was constant irrigation of wounds with water, or the immersion of the wounded part in a water bath. The bath gave excellent results in the hands of Vallette and others, especially when combined with the use of various substances which we now know to possess antiseptic properties, such as tincture of benzoin, creosote, and iron salts.

About this time also subcutaneous surgery was introduced, but unfortunately it was a method applicable only in a very limited number of cases. John Hunter had at an earlier date pointed out the advantage of healing by scabbing, and to obtain this became a frequent object in the treatment of small wounds. Nevertheless the most common method of treating wounds was, perhaps, by a water dressing, a piece of lint dipped in water being applied over the surface of the wound, and covered by oiled silk. This method led to putrefaction and suppuration in the wound in the great majority of cases.

Shortly before Lister began his work some surgeons had begun to employ various substances, with the avowed intention of diminishing the putrefaction of the discharges in wounds. Among the materials thus employed were alcohol, glycerine, chlorine compounds, iodine, chloride of iron, coal-tar preparations, and even carbolic acid. But the methods followed in the employment of these substances were imperfect, and, not being founded on any precise knowledge of the causes of putrefaction, they failed to ensure the desired result.

The method which Lister himself employed before he took up antiseptic work is thus described by Sir Hector Cameron, who was his dresser and house surgeon at the time he began his antiseptic work :—

He was in the habit at this time of treating all recent wounds by the simple plan which had been for many years taught and practised by Mr. Syme in the Edinburgh Hospital. After the principal arteries had been secured by ligaturing them with well-waxed silk strings, and smaller bleeding-points were arrested by torsion as originally suggested by Amussat, two folded pads of lint were placed on each side of the lips of the wound so as to exercise pressure, while a larger piece of the same absorbent material was placed over these, and secured by a fairly firm bandage. Drainage was effected by bringing the ends of the long silk ligatures out at one or both ends of the wound, and the sutures used were of silver wire. This dressing was left undisturbed for several days, unless a complaint of pain or a quickened pulse demanded earlier interference. Occasionally, union by first intention occurred except in the tracks of the ligatures, but so long as these remained there was no security against the supervention of one or other of the many hospital diseases which were always present in the wards. More often the wound—whatever its original nature—inflamed and suppurated freely ; it was then treated either with water dressing covered by gutta-percha tissue, or poulticed with linseed-meal poultices. In either case, the coverings of the wound were frequently changed, and at each renewal the pus was squeezed out as thoroughly as possible (counter openings being made if necessary), and the wound well washed with a mixture of warm water and Condy's Fluid, usually poured out of a kettle. Lister soon began to enjoin on all persons in his clinique the practice of scrupulous cleanliness, which was at that time by no means always a characteristic of surgical practice. The washing of hands was insisted on after dressing each individual case, and large piles of clean towels stood on the tables of his wards for the use of his dressers and nurses.

In consequence of the reported results of some experiments on dogs by Polli of Milan, he tried at this time the free exhibition of sulphite of soda or potash in solution as a cure and also as a prophylactic of pyaemia and other septic diseases. Every patient operated on or admitted to his wards with a wound had this remedy administered to him in suitable doses from the very first, and it was also used largely in washing and dressing wounds. All these, and many other attempts to improve the salubrity of his wards, unfortunately availed little or nothing.

Cameron ends his description of the treatment of wounds at that time as follows :—

When I first became a dresser, the carrying out of such details was my daily occupation. Every wound discharged pus freely, and putrefactive changes occurred in the discharges of all, producing in the atmosphere of every surgical ward, no matter how well ventilated, a fetid sickening odour, which tried the student on his first introduction to surgical work just as much as the unaccustomed sights of the operating theatre. It is hardly necessary to add that fatal wound diseases and complications were never absent at any time from the hospitals of that day.

Such then was the state of surgical practice about the time when Lister began his work. From his student days, the subjects which had most attracted his attention were inflammation and the general septic diseases which so constantly followed the infliction of wounds, and when he commenced surgical teaching in Edinburgh the nature of inflammation occupied a very prominent place in his lectures as in his thoughts. Being dissatisfied with the views held at that time, he proceeded to investigate the subject for himself, and produced his classical papers on the early stages of inflammation, on the pigment cells of the frog, and on the nervous regulation of the arteries; subsequently, as has been mentioned above, his attention was turned to the subject of coagulation of the blood, and to the behaviour of blood in healthy and diseased blood-vessels. But although these investigations furnished most important results and were of inestimable value in his subsequent work, yet they did not directly lead him to the antiseptic principle in surgery.

In spite of the light thrown on inflammatory processes by his researches there still remained the fact that inflammation and suppuration constantly occurred after the infliction of open wounds, and that the various septic diseases frequently attacked the simplest wounds and rendered the most skilful operations unavailing. Most surgeons had become resigned to the occurrence of inflammation and suppuration in wounds, and looked on them as natural and inevitable consequences. Many indeed regarded the occurrence of 'healthy' suppuration as a thing to be desired, because it was observed that once suppuration was established the patient's condition improved. It was therefore assumed that the sooner suppuration occurred the better. Hence the aim of many was to hasten the formation of this 'laudable' pus, and at the same time to control 'the excessive action' in the wound which was supposed to lead to the various septic diseases.

This was not Lister's view. His ideal of what should happen in a wound was what occurred in a subcutaneous injury such as a simple fracture, in which repair took place without any inflammation, suppuration, constitutional disease, or general sepsis. In his opinion the occurrence of inflammation and suppuration in a wound was by no means a desirable thing, but was, in fact, contrary to the natural processes, as exemplified by subcutaneous injuries, and was therefore to be avoided rather than aimed at.

At an early period Lister had come to recognise that the essential cause of the troubles after operations and injuries was in some way or other connected with the putrefaction of the blood and discharges in wounds. Putrefaction did not occur in subcutaneous injuries, or in wounds which healed by first intention, and in these there were no septic troubles, while conversely, as soon as putrefaction appeared, inflammation and other septic diseases followed. He concluded, therefore, that these complications were due to the formation of irritating materials in the discharges of the wounds as the result of putrefactive fermentation, and that the aim of treatment should be to get rid of the putrefactive process.

In his Huxley Lecture[1] he refers to the treatment of hospital gangrene while he was house surgeon to Mr. Erichsen, and it is clear that even then he looked on the various diseases of wounds as essentially the result of putrefaction of the discharges. At that time the general teaching was that these putrefactive changes were the result of the action of the air, and more especially of the oxygen, on the organic fluids present in the wounds. He was never satisfied with this explanation ; like John Hunter, he was at an early period puzzled by a case of general surgical emphysema after fracture of the ribs with puncture of the lungs, for although air was present in the tissues and in contact with a large amount of blood, putrefaction and septic troubles nevertheless did not occur. This puzzle was constantly present in his mind until the solution was revealed by the researches of Pasteur.

It is interesting to note in passing that even after the introduction of antiseptic surgery, some surgeons, unwilling to give up the oxygen theory, spoke of the antiseptic dressings as 'occlusive', their assumption being that the dressings excluded oxygen. Lister himself always recognised the hopelessness of any attempt to exclude oxygen, and never made any efforts in that direction. He had already, as has been pointed out, tried to mitigate the putrefactive process by scrupulous cleanliness, insisting on the washing of the hands between the dressings, a plentiful supply of towels in the wards, and the use of various substances which we now know to possess antiseptic properties. No appreciable improvement resulted, and it was perhaps fortunate for the development of antiseptic surgery that Lister's wards were so insanitary that these attempts at cleanliness were of little avail. It is important to remember this fact, for the considerable improvement which in numerous instances followed on the recognition of the great importance of scrupulous cleanliness, led many surgeons to attribute the good results of antiseptic surgery entirely to simple cleanliness and not to the destruction of bacteria.

At this time (the early 'sixties' of the last century) Lister, then Professor

[1] Vol. ii, p. 515.

of Surgery in the University of Glasgow, was constantly speculating on these matters, especially on the cause of the putrefaction of the discharges in wounds, and during one of his discussions with friends the suggestion was made that the perusal of Pasteur's papers on fermentation and spontaneous generation, which had then recently appeared, might be of assistance to him. This suggestion was fertile, and it may well be imagined how great a revelation to Lister were these researches of Pasteur. The oxygen theory of putrefaction, which had seemed to oppose all advance, was at once swept away, and the problem was now seen to be not to exclude intangible gases, but to deal with living organic particles which could be destroyed and the characteristics of which could be carefully studied.

It is interesting to note that previous to the appearance of Pasteur's work three papers had been published which really laid the foundation of the germ theory and of modern bacteriology; these were by Schultze in 1836, Schwann in 1837, and Cagniard-Latour in 1838. The two latter authors brought forward a large amount of evidence which satisfied them that the alcoholic fermentation of grape-juice was due not to oxygen but to the growth in the fluid of the *Torula cerevisiae*. Schwann also studied the putrefactive decomposition of meat-juice and other organic substances, and came to the conclusion that it was not the gases of the air which caused these changes, but organic particles which floated in the air, and could be destroyed by heat. He went further and ascribed all fermentative processes to the growth of the organisms found in fermenting liquids. In 1854 additional evidence was brought forward by Schröder and Dusch, who showed that it was not necessary, following the example of previous observers, to calcine the air which had access to the flasks, but that putrefaction did not occur in organic fluids contained in flasks if the air entering the flasks were filtered through cotton-wool. Pasteur finally (1864) completed the proof by showing that it was not necessary either to heat the air or to filter it before admitting it to properly prepared organic fluids, but that if it were conducted along a tortuous tube in which the dust could settle before it reached the fluid, no change took place in the organic matter. He showed also that if flasks containing putrefactive material were left open in a place where the air had been undisturbed sufficiently long to allow the dust to settle, as, for example, in a cellar, no decomposition took place, nor did any micro-organisms appear in the fluids.

Apart from these researches on the causes of fermentation, much heated discussion had gone on for many years as to the significance of the minute 'animalculae' which appeared in decomposing fluids, and the question whether these organisms originated *de novo* from the organic fluids in which they were found, or whether they always came from pre-existing organisms which had somehow or other gained admission to the fluids, had been warmly debated. Pasteur's work, however, really struck the final blow at the doctrine of spontaneous generation, although many further convincing proofs were brought forward later by other experimenters, notably by Tyndall and by Lister himself.

The information, then, which Lister obtained from studying Pasteur's work was (1) that organic fluids which had been boiled but were still prone to the development of organisms and to fermentative changes, could be preserved without any change if the air admitted to the material after boiling had been calcined, or filtered, or had been kept at rest so long, or reached the fluids so slowly, that all the dust had had time to settle; (2) that the organisms found in the decomposing fluids were not produced spontaneously by changes in albuminoid materials, for they might appear and grow in artificial fluids containing mineral substances only; (3) that these organisms were present in the dust of the atmosphere, and in that deposited on surrounding objects; and (4) that the decomposition of the organic fluids coincided with the development of these organisms. If they were absent, no decomposition occurred; as soon as they were admitted and began to grow, fermentative changes appeared.

This was the work to which Lister's attention was called, and it is easy to imagine the flood of light thrown on the whole subject of decomposition in wounds by its perusal. Lister at once applied himself to the task of finding some means of preventing the development of these living organisms in wounds. He formulated the hypothesis that the inflammation and septic diseases which occurred after wounds were due to the putrefaction of the discharges of the wounds; while this putrefaction was in its turn due to the entrance of living micro-organisms from the air, and from the dust on surrounding objects. He made the deduction that if the access of living organisms could be prevented, and their growth in wounds arrested without at the same time damaging the wounds seriously by the means employed for this purpose, an open wound would follow the same course as a subcutaneous injury. No doubt this first conception was incomplete, but it was thoroughly sound, and while subsequent work has enormously extended the facts, the basal idea that it is the entrance of organisms into the wound from without which produces the inflammatory and septic troubles, and that therefore the aim of treatment must be to exclude or destroy them or inhibit their growth, still remains the fundamental principle of the treatment of wounds. The great variety of bacteria which may enter wounds, their very different behaviour, their various pathogenic properties, their origin, and the reaction of the tissues to their growth, are all subsequent developments which have had their influence on the details of the method, but which have in no way affected the original Listerian principle.

With the light thus shed on the problems on which he had been pondering for years, Lister at once threw all his energies into the application to the treatment of wounds of the principle established by these researches *in vitro*. It was evident that filtration of the air which reached wounds was not a practical plan, nor could heat be used to destroy the organisms in all places from which they might contaminate the wounds, for these organisms were not merely floating in the air, but were deposited on all surrounding objects, and to operate in an atmosphere of filtered air, or of air previously subjected to heat, could not meet the requirements of the case. Hence he turned to the search for chemical substances which possessed the power of destroying these living particles. About that time experiments had been made at Carlisle on the disinfection of sewage by German creosote, the active agent in which was crude carbolic acid; the interesting results so obtained suggested to Lister that this substance might serve his purpose, and he accordingly procured a supply. He determined to test the new principle first in the treatment of compound fractures, the results in these injuries being especially bad at that time in his wards. He had to wait some months before he could put his ideas into practice, but at length the opportunity came, and on the 12th of August, 1865, he was able to put the matter to the test, with results which amply justified his hypothesis. It is very curious that the material thus more or less accidentally selected in the first instance as an antiseptic has turned out to be the most suitable of any yet known and tested for various purposes in connexion with the asepsis of wounds, especially for the disinfection of the skin.

Now followed a period of the most remarkable activity, involving an amount of mental exertion and patient toil which probably no other man would have had the genius or indeed the physique to carry through. Lister came to this work equipped in an entirely exceptional manner. Endowed with extraordinary mental insight, and provided with much physiological and chemical knowledge, he had spent years in considering and investigating the subject of wounds, and he was thus able to grasp the significance of the numerous new phenomena which he observed while carrying out his methods of treatment. During this early period every case contributed fresh information, and led to constant improvement in his attempts to imitate nature's processes, and this constant modification of his methods in accordance with fresh observations is remarkable evidence of his clearness of vision, and a striking proof of the elasticity of his mind and of the absence of bias. To the very end of his active work as a surgeon he was never entirely satisfied, but was always straining for something better, having ever in mind his one great ideal of making the conditions existing in an open identical with those in a subcutaneous wound.

This activity took three great directions: (1) bacteriological work, especially in connexion with the germ theory of putrefaction; (2) constant striving after improvements in the methods employed in carrying out the principle which he had laid down as essential in the treatment of wounds; and (3) improvements in the treatment of various diseases and injuries, rendered possible by the fact that operations had lost their greatest dangers.

BACTERIOLOGICAL WORK

In the early days Lister did a great deal of bacteriological work, partly in order to satisfy himself as to the accuracy of the theory on which he had based his system of treatment, and partly to test suggested alterations in his methods. Very little of this work has been published, indeed most of it was never intended for publication, but what he has written shows the impress of his genius. He repeated Pasteur's experiments, especially that of the flask with the contorted neck, and he showed that the same results might be obtained by another method, namely by the use of glasses provided with loosely fitting glass covers.[1] He also pointed out the importance of properly sterilizing by heat all vessels employed in these experiments, and he introduced the methods of dry sterilization which are still employed for this purpose.[2] He devised a flask for the storage of organic fluids and also methods of filling tubes and vessels from these flasks, which are most valuable when working with fluid media.[3]

Perhaps his most important work in pure bacteriology was that on lactic fermentation. In that he obtained for the first time a pure cultivation of a single species of bacterium (*Bacillus lactis*), and he demonstrated that the lactic fermentation was due to the growth of this organism in milk. In this connexion he devised a plan of separating different kinds of bacteria from one another by repeated dilution which, though very laborious, remained practically the only satisfactory means of obtaining pure cultures till the introduction of Koch's method of cultivation on solid media.

Experiments were also made on the sterility of the natural fluids of the body, such as milk and urine, before they came into contact with the external air. A great deal of work was done in the way of testing new antiseptics and the value of different dressings, in fact almost every one of the later stages in his methods was tested in this way. Very interesting also is his work on the value of

[1] Vol. i. p. 279. [2] Vol. i, p. 278. [3] Vol. ii, p. 55.

the inhibitory action of antiseptics on the growth of bacteria, as distinguished from their destructive action.[1]

Apart from these experiments *in vitro*, it must be realized that the introduction of the antiseptic system was one vast experiment on the living body. Up to that time, with perhaps the exception of observations by Davaine upon anthrax, no work had been done which demonstrated any pathogenic action of bacteria. Indeed during the early development of antiseptic surgery the question of pathogenic bacteria, as we now know it, did not arise. In the first instance it was 'putrefaction' in the discharges of a wound which was attacked, and though this was looked on as due to the bacteria present in these discharges, no classification of these bacteria into species was thought of, and no differentiation into pathogenic and non-pathogenic organisms was made. It was simply a case of preventing the entrance of bacteria as a class into wounds and their development there. Very soon, however, we find Lister pointing out that there must be different species of bacteria, and that putrefaction was not the only injurious fermentation which might occur in wounds, for he noted that in some cases, although there was no odour in the discharges, suppuration nevertheless occurred; thus, in a footnote to a paper published in 1870[2] he says: 'This group (cases of putrefactive suppuration) ought to include the products of other ferments besides those of putrefaction, for I am satisfied that inodorous ferments sometimes occur in the animal fluids and produce salts which stimulate to suppuration; also viruses inducing suppuration are very probably of the same essential nature (ferments), though some at least are odourless, as in the case of erysipelas.' It is true that he attributed the odourless suppuration in some of these cases to reflex disturbance of the nervous system, produced, for example, by tension in the wound, yet at the same time he recognised that, in some instances at any rate, it was due to bacterial infection. Indeed it was more especially with the view of demonstrating that there are different kinds of bacteria, each with its own fermentative action, that he undertook his work on lactic fermentation. Very soon also we find him beginning to realize the possibility of the penetration of bacteria into the body from the wound, and thus the distinction between pathogenic and non-pathogenic bacteria.

Under the system he evolved not only did inflammation and suppuration disappear, but also pyaemia, hospital gangrene, erysipelas, and tetanus. In his demonstrations at the hospital he was fond of pointing out how erysipelas spread like fairy rings, as if the organisms which produce it were advancing in the tissues before the redness and dying out behind it, a view strikingly confirmed subsequently by Koch and others. He also remarked, with some diffidence it is true,

[1] Vol. i, p. 278.

[2] Vol. ii, p. 140.

on the disappearance of tetanus from his wards, as if that also were a disease due to bacteria.

Another subject on which he soon began to speculate was the protective arrangements of the body. He succeeded in preserving urine and milk from alteration without subjecting them to any preliminary treatment by boiling or otherwise, thus showing that bacteria did not penetrate along healthy canals, such as milk-ducts. This he attributed to the destructive action of the healthy living organism on the bacteria, and he pointed out that in wounds also it was capable, to a certain extent, of disposing of micro-organisms. Although Lister did not do any experimental bacteriological work on animals, there is no doubt that the remarkable results obtained by his methods of wound treatment, and the energy and insight with which he laid stress on bacteria as the cause of the grave troubles following wounds, had a most important influence on others, leading them to the study of the pathogenic effects of bacteria, and thus served to stimulate the rapid development of the science of bacteriology.

THE DEVELOPMENT OF THE ANTISEPTIC SYSTEM[1]

We have already traced matters up to Lister's first application of his views to a case of compound fracture. That compound fractures should have been the form of injury selected by Lister as likely to afford the most suitable test of his hypothesis is not difficult to understand when it is remembered how great was the contrast in those days between the course followed respectively by simple and compound fractures. The latter were indeed the most fatal of all surgical injuries, and accounted for a large proportion of the cases of pyaemia which were of such frequent occurrence in all hospitals.

The object aimed at being the prevention of the putrefaction in the wound brought about by organisms introduced either at the time of the accident or subsequently during the course of the treatment, means were taken to obviate both dangers. The first indication was fulfilled by introducing into the wound a pledget of calico or lint held in a pair of forceps and saturated with undiluted crude carbolic acid; with this all the interstices of the wound were thoroughly swabbed out. The second indication was met by placing over the wound, and overlapping it in all directions, for about half an inch, a double layer of lint saturated in the same material. This lint was covered by a piece of thin block-tin or sheet-

[1] In this section the history of the evolution of wound treatment which Sir Hector Cameron has given in his James Watson Lectures before the Faculty of Physicians and Surgeons of Glasgow has been largely drawn upon, and to that volume readers who desire a fuller guide to Part III of these collected papers are referred (*Lord Lister and the Evolution of Wound Treatment during the last Forty Years.* Glasgow. J. MacLehose & Sons. 1907. Post 8vo, pp. 96). See also vol ii. pp. 349, 365.

lead, moulded in a concave form so as to fit over the mass of lint. It was fixed in position by strips of adhesive plaster, the limb being placed in suitable splints. The carbolic acid and blood mingling in the small piece of lint formed a thick paste, and converted the whole into a sort of crust or scab, which adhered to the wound with great tenacity. Once a day the tin cap was removed, and the crust of lint and blood was painted over lightly on its outer surface with carbolic acid. What was aimed at was to keep this crust from becoming septic, while its under surface in contact with the wound, becoming gradually free from the carbolic acid which it at first contained, should cease to be irritating in itself, and therefore no longer interfere with the process of healing. The dressing was of the nature of an artificial scab, but with this difference, that the substance of the scab was charged with an antiseptic introduced with the object of destroying any germs of putrefaction which might find their way to the scab from the skin, or from the splints padded with soft absorbent material to receive such bloody discharges as oozed from the wound during the first day or two. It was, however, recognised that the vapour of the carbolic acid retained under the cap of tin interfered with the process of cicatrization, and therefore, after it seemed likely that the wound was so far repaired as no longer to communicate with the seat of fracture, the antiseptic crust was detached, and the final closure of the surface wound allowed to take place under some simple form of dressing.

The results of the application of the principle to the treatment of compound fractures could not have been more striking, for the patients suffered neither from putrefaction and inflammation in the wound nor from general septic diseases. The necessity for primary amputation in the majority of cases disappeared, many limbs and lives were saved, and the treatment of these injuries underwent a radical change.

There is no instance in the history of surgery, and indeed few in the history of science, in which a deduction has been so completely verified when put to the test.

Its success in this particular class of cases naturally suggested and even urged the extension of the principle to others, and it was not long before an opportunity occurred of employing it in a case of psoas abscess, an affection from which at that period few adults recovered, while it was only slightly less fatal in children. The patient was a middle-aged woman, and the abscess, which was pointing in one loin, was about to burst. It was incised, and some of its thick contents mixed with the crude carbolic acid; two pieces of lint soaked in this mixture were laid over and around the wound and covered with a cap of block-tin. When the dressing was removed next day, there was no escape of pus as was usual under the treatment then customary, and pressure caused only a drop or two of serous fluid to exude. This result, though highly satisfactory, produced a momentary embarrassment, for there was no pus or blood with which to mix the carbolic acid for the new dressing. This difficulty was overcome by thickening a solution of carbolic acid in boiled linseed oil (1 in 4) with whitening (carbonate of lime). This putty-like material was spread upon a piece of block-tin and laid over the incision, care being taken that this dressing overlapped it widely in all directions; it was fixed in position by strips of adhesive plaster, and an absorbent compress was bandaged over all. The dressing was renewed daily. The result was entirely satisfactory; the abscess cavity remained free from any septic change, and eventually healed, having yielded no pus from first to last, but only a steadily diminishing quantity of clear serous fluid.

This case taught many important lessons; it not only afforded a fresh proof, under slightly different conditions, of the truth of the theory, but was the first demonstration of facts since grown familiar, but which could not then certainly have been foretold. These were that after the original contents of an abscess, whether acute or chronic, were evacuated, if changes in its interior resulting from contact with outside morbid agents be avoided, instead of pus only a thin serous fluid would be discharged and would rapidly diminish in quantity; that in consequence it was neither essential to open the abscess at a dependent part, nor necessary to make counter-openings; that under such circumstances no constitutional disturbance need be feared; and lastly, that such abscesses, if a careful course of antiseptic treatment were persevered in, might be expected to close permanently.

A purer specimen of carbolic acid was obtained before long and found to be soluble in water in the ratio of one part in twenty (five per cent.). After the introduction of this carbolic lotion the method followed in the treatment of compound fracture was first to wash out the interior of the wound thoroughly with a five per cent. solution of the acid, and then to cover its surface with a piece of lint saturated with carbolic oil (1 to 4) large enough to overlap it in every direction; over this was put a large dressing of the putty, smoothly spread on calico to the thickness of about a quarter of an inch. At first, a further covering of block-tin was employed, but its use was afterwards dispensed with as unnecessary. The dressing of putty was changed daily, but the piece of oiled lint, soon saturated with blood, was left next the wound, harbouring under it a crust of blood of greater or less thickness. It became usually fairly dry, and when the time arrived for removing the crust and discontinuing the splints, either a firm cicatrix or a superficial granulating sore was exposed to view. In opening an abscess a large piece of lint soaked in a solution of carbolic acid (1 to 4) was placed over the portion of the skin to be incised and left for a little to act upon it. The lower edge of it was then raised, the incision made, and the curtain of lint let fall, the abscess being evacuated by gentle pressure under its protection. The antiseptic was not injected into the cavity of the abscess, experience having shown that while such injection was quite superfluous, it could only do mischief by causing irritation. A narrow strip of lint dipped in the same oily solution was introduced through the incision to prevent primary union and at the same time to act as a drain. On removal of the oily antiseptic curtain a dressing of the putty, spread on a piece of block-tin, was immediately fixed over the incision by adhesive plaster and bandaged to the part. The thin discharge flowed out beneath the edges of the putty, which was renewed once a day.

The use of block-tin was not long continued: the putty was spread upon calico, and in this form the dressing was extended to the treatment of incised wounds made by the surgeon. Although the results obtained with this antiseptic putty dressing were strikingly satisfactory, its employment was attended by certain practical inconveniences, and Lister devoted a great deal of patient research to devising a substitute which should be not less effective to achieve the main object in view, but more convenient in use. After many experiments, he found a suitable material in shellac prepared in the following manner. When mixed with carbolic acid (1 to 4) shellac forms a flexible mass from which, as from a reservoir, the acid is constantly and not too rapidly given off. The practical objection to its use in this form was that it adhered too firmly to the skin, but this was overcome by spreading the mixture on calico and then painting a solution of india-rubber in benzene over the surface. The thin layer of india-rubber left on the surface of the shellac when the benzene evaporated prevented the plaster sticking to the skin, while the carbolic acid as it was liberated from the shellac passed freely through it. This new dressing presented many practical advantages. It was not disintegrated by friction like putty, and being much lighter was not only far less cumbrous, but could be more easily maintained in position; while, further, it was always ready for use, whereas the putty had to be specially prepared by the surgeon on each occasion. It was adopted alike for the treatment of injuries, abscesses, and incised wounds. In the last the method of treatment was as follows: During the performance of an operation the wound was from time to time irrigated with carbolic lotion, and more especially was filled with this lotion while it was being stitched up. The lotion was then expressed from the wound, the lac-plaster immediately applied, overlapping the surface to a considerable area around the wound, cloths being placed about the margin in order to absorb the discharge that passed out from under the lac-plaster. Attention was also paid to the drainage of wounds, and for this purpose a strip of lint soaked in a solution of carbolic acid and oil (1 to 4) was inserted at one angle of the wound and retained for at least forty-eight hours.

It will be observed that these early antiseptic dressings were not absorbent, and were therefore impervious to the discharges from the wound. Though the carbolic acid they contained could not be washed out of them, however great the flow of blood or serum in the early stage, it was constantly given off, thus preventing the entry of infective organisms. The fluids of the wound were, alike by the putty and the lac-plaster, shed from it in an antiseptic atmosphere maintained between the dressing and the skin by the carbolic acid slowly and constantly liberated from the putty or lac. Under the lac-plaster the wound healed without a scab.

The favourable reports of some surgeons on the use as an antiseptic dressing of oakum carefully selected and teased into a fine soft uniform mass next induced Lister to consider the advantages of a dressing which would absorb the fluids of a wound instead of distributing them. His previous objection to the use of porous dressings was founded on the observation[1] that the discharge, if at all free, washed out the antiseptic from the fibres of the material used and, by leaving over the wound a dressing devoid of any antiseptic, opened up the way for the penetration of putrefaction. In oakum, however, each fibre was imbued with the antiseptic (creosote) in an insoluble vehicle, so that the discharge could not wash the antiseptic out of the fibres any more than in flowing beneath the lac-plaster, to a narrow strip of which each individual oakum fibre might fairly be compared.

While impressed with the advantages of an absorbent material thus thoroughly imbued with an antiseptic which would not be washed out of its fibres by the discharges, Lister preferred to devise a dressing in which the proportion of the antiseptic could be accurately adjusted, and free from certain minor practical drawbacks which attended the use of oakum. This led to the introduction of the gauze dressing, which in one form or another has since been and still is used all the world over, either charged with some antiseptic substance or sterilized by heat. A cheap muslin of open texture, known in the trade as 'book-muslin', was charged with resin, paraffin, and carbolic acid. Resin, which is one of the principal constituents of ordinary oakum, holds carbolic acid with great tenacity, so that a mixture of one part to five does not, if applied to the tongue, produce any undue sense of pungency. The paraffin was added to obviate the objection that this mixture was very sticky, as well as apt to be irritating to many skins. The melted ingredients were mixed in the proportion of one part of the acid to four respectively of resin and paraffin, and the mixture was diffused through

[1] Vol. ii, p. 168.

the fibres of the cloth. This antiseptic gauze had carbolic acid thus fixed in every fibre, while the fine spaces between, which give its porous character to the cloth, were still open for the discharge to pass through. It was folded in such a way as to make a thickness of eight plies and placed over the wound, overlapping it widely in all directions. But in order to prevent fluids from going straight through the eight plies of gauze and possibly exhausting its antiseptic ingredient at that part, a piece of very thin macintosh or jaconet, previously washed in the antiseptic lotion, was incorporated with the mass of gauze by being slipped under its top layer, thus leaving seven layers of the gauze next the wound, and compelling the discharges to make their way to the margins of the dressing, instead of coming straight through.

As has already been said, the whole aim of Lister's work was to bring about and maintain in an open wound conditions similar to those which exist in a subcutaneous injury, and from the first he fully recognised that while fermentative changes were the most important they were not the only sources of irritation—that in fact the chemical substance employed to prevent fermentation was also more or less irritating, and interfered with the attainment of his ideal. He therefore now directed his attention to devising means of diminishing or altogether avoiding irritation of the wound by the carbolic acid contained in the dressings. The irritation produced by the antiseptic which came into contact with the wound during the operation was only temporary. The carbolic acid when mixed with the blood lost much of its irritating character, and was moreover absorbed, and disappeared from the wound in a comparatively short time. When once the wound had been closed at the operation, Lister considered it unnecessary to irritate the line of incision or the interior of the wound by subsequent applications of the antiseptic. He therefore never syringed out a wound at a subsequent dressing, as some surgeons were fond of doing; the utmost he did was to have some carbolic lotion flowing over the line of incision and the adjacent skin while the dressings were being changed. This lotion did not penetrate into the interior of the wound, and acted on the surface only for the brief period during which it was exposed. Nevertheless he recognised that the carbolic-acid vapour coming off from the gauze or the lac-plaster was irritating to the line of incision, and therefore he made numerous experiments with the view of finding some material more or less impenetrable to the vapour of carbolic acid, which might be placed directly over the wound below the carbolic gauze, but widely overlapped by the absorbent antiseptic gauze dressing. Though the vapour of carbolic acid passed easily through gutta-percha tissue and thin sheets of indiarubber, the common oil-silk used for covering water dressings was found to be much less penetrable by it. Taking this as a basis, he covered it with copal

copal, which was found to offer even stronger opposition to the passage of carbolic acid than oiled silk itself, and lastly, painted over both a solution of dextrine, which permitted the surface to be uniformly wetted. Before being applied to the wound this 'protective plaster' was dipped in a solution of carbolic acid. The acid was soon dissipated, and the plaster became an unstimulating covering to the wound, defending and protecting it from the direct action of the superimposed and widely overlapping antiseptic dressing, but in no way interfering with the outflow of the blood and serum.

While these improvements in the material of the dressings and their manner of application were in progress, another question had been engaging Lister's attention, and had been the subject of much thought and experimental inquiry. From an early stage he had seen that if the full advantages of the antiseptic system and all that it implied were to be realized in general surgical treatment, the method of arresting haemorrhage, and especially the kind of ligature used, must be reconsidered. He had very early obtained evidence that blood-clot could, in the absence of fermentative changes, undergo organization. In 1867[1] he placed on record the following observation: 'I was detaching a portion of the adherent crust from the surface of the vascular structure into which the extravasated blood beneath had been converted by the process of organization, when I exposed a little spherical cavity about as big as a pea, containing brown serum, forming a sort of pocket in the living tissues, which, when scraped with the edge of a knife, bled even at the very margin of the cavity. This appearance showed that the deeper portions of the crust itself had been converted into living tissue. For cavities formed during the process of aggregation, like those with clear liquid contents in a Gruyère cheese, occur in the grumous mass which results from the action of carbolic acid upon blood; and that which I had exposed had evidently been one of these, though its walls were now alive and vascular. Thus the blood which had been acted upon by carbolic acid, though greatly altered in physical characters, and doubtless chemically also, had not been rendered unsuitable for serving as pabulum for the growing elements of new tissue in its vicinity.' He also made an observation which was quite novel at the time, that a piece of dead bone which lay exposed in the wound of a compound fracture, instead of being exfoliated as would have occurred in a septic wound, became absorbed.[2]

These and other similar observations raised the question whether ligatures might not be cut short and left in the wound, for it seemed reasonable to hope that, just as dead bits of tissue had been disposed of by absorption, so more or

[1] Vol. ii, p. 8. [2] Vol. ii, p. 16.

less slender threads of organic material, prepared so as to be free from septic organisms, might be similarly removed.

Lister's experiments and observations on this subject are fully recorded in papers printed in volume ii. He first, on the 12th of December, 1867, tied the left carotid artery of a horse with purse-silk which had been steeped in a strong watery solution of carbolic acid;[1] the ends were cut short, and the wound, which was dressed antiseptically, healed immediately. Six weeks later the horse died, and on laying open the vessel there was found at the cardiac side of the ligature a firm adherent clot, an inch and a quarter long, but at the distal side coagulation had been entirely prevented by the reflux current of blood through a branch about as large as the human vertebral artery, which took origin as close to the ligature as possible. Under such circumstances secondary haemorrhage would certainly have occurred had a thread been applied in the manner then commonly employed. But in this specimen the artery appeared as strong at the part tied as elsewhere. The cul-de-sac showed some irregularity due to puckering of the internal and middle coats, but the surface appeared completely cicatrized, and presented the same character as the natural lining membrane of the vessel, and the ligature, which seemed as yet unaltered, was found lying dry in a bed of firm tissue. The tissue within the noose was apparently a new formation in place of the portion of external coat killed by the tightly tied thread; externally, the constriction, necessarily caused in the first instance by tying the ligature, had been filled in by a similar compact structure.

The success of this experiment justified the application to man of the principle upon which it was based. Accordingly, when a few weeks later (29th of January, 1868) Lister was called upon to tie the external iliac artery for aneurysm of the common femoral artery in an elderly lady, he made use of a silk ligature steeped in undiluted carbolic acid, used sufficient force to divide the internal and middle coats of the artery, cut the ends of the ligature short, and dressed the wound antiseptically. The aneurysm consolidated, the wound healed without suppuration, and the patient was out of bed in four weeks, and was able to take outdoor exercise in two more. Within a year she died suddenly from rupture of an aortic aneurysm. Careful examination of the iliac artery after death showed that the knot of silk was still in great part present, enclosed in a thin-walled capsule. Besides the remnant of the ligature, the tiny capsule contained a minute quantity of yellowish semi-fluid material, looking to the naked eye very like thick pus. Microscopic examination, however, proved that pus corpuscles formed but a small proportion of its constituents, which were principally rounded corpuscles of smaller size, and fibro-plastic corpuscles, together

[1] Vol. ii, p. 64.

with some imperfect fibres and granular material. There were evidences of the silk having been eroded by the action of the tissues around it, pieces of its fibres being present in the puriform fluid ; they had not been materially softened, but only ' superficially nibbled, so to speak. Indeed,' Lister added, ' considering the organic character of silk, the remarkable thing seems to be, not that it should be absorbed by the living tissues, but that it should resist their influence so long.'

The local result in this case was thus not altogether satisfactory, and Lister therefore turned his attention to other materials. Animal ligatures of various kinds, catgut, tendon, and leather, had long before been tried and abandoned as unsatisfactory, but there was good reason to expect that in the absence of sepsis very different results would ensue. Lister had been struck by the fact that the sloughs and clots produced by the injection into naevi of strong solutions of perchloride of iron or tannic acid, though impregnated with these substances, yet rapidly disappeared without suppuration. He had also learnt that portions of dead tissue and of blood-clot, free from sepsis, were absorbed, and that this process was in no way interfered with when carbolic acid had freely acted upon them. There seemed, therefore, to be no reason why carbolic acid should not be used for disinfecting the animal ligature.

In his next experiment, in which (on the 31st of December, 1868) he tied the right carotid of a calf at about the middle of the neck, he applied two ligatures separated from each other by a distance of about an inch and a half. One was composed of three strips of peritoneum from the small intestine of an ox, twisted into a cord, the other was of fine catgut. Both had previously been soaked for four hours in a saturated watery solution of carbolic acid. The wound healed by first intention, and the calf was killed a month afterwards. The result of the dissection of the vessel was at first disappointing, for the ligatures were still to all appearance present and as large as ever ; more minute examination showed that in reality they had been absorbed and replaced by bands of living tissue, ' the growing elements of which had replaced the materials absorbed, so as to constitute a living solid of the same form '. The fleshy bands so formed were continuous with the arterial walls, and so far from weakening the vessel at the point of ligature had rather strengthened and reinforced it, while by the early healing of the wound an immediate reconsolidation of the tissues detached from the vessel had taken place. The evidence of the organization of the ligatures, clear to the naked eye, was abundantly confirmed by the microscope. All these facts seemed to give sure promise, as indeed has proved to be the case, of security against secondary haemorrhage, so frequent and so justly dreaded up to that time, as well as of the absence of suppuration in connexion with such ligatures.

Lister subsequently gave much time and thought to the discovery of the best methods of preparing the catgut ligature so as to meet the various conditions which were required, and his latest contribution to the subject was in fact published so recently as the 18th of January, 1908.[1] The raw catgut as obtained from the shops was unsatisfactory, for the ligature as soon as it became soaked with fluid, and especially with serum, swelled up, and the knots became untied; further, it was absorbed too rapidly, a most serious drawback. The chief points to which he paid attention in the preparation of catgut suitable for general surgical use were the breaking strain, the solidity and permanence of the knot, the pliability of the material, and the rapidity of its absorption in the tissues; the papers in which he described the different methods devised for attaining these objects are reprinted in the second volume. At the present time, in the preparation of catgut attention is directed chiefly to its sterilization, without special reference to the other essentials on which so much stress was laid by Lister, but it may be doubted whether this is wise, and whether any better material than Lister's sulpho-chromic catgut has been introduced.

The adoption of absorbent dressings and absorbable ligatures marked a distinct stage in the development of antiseptic surgery; by simplifying the technique and rendering the results surer in the hands of other surgeons, it greatly contributed to bring about the general adoption of the system, and paved the way for the extraordinary extension of the field of surgery which the next quarter of a century was to witness.

At about the same time the metallic suture ceased to be the sole method of closing the wound, giving place to more convenient stitches of silk. In 1870[2] Lister gave an interesting account of the methods he employed in stitching up a wound, especially in those cases in which a portion of the skin had been removed, and where, therefore, there was considerable tension at the edges of the wound. The silk was rendered aseptic by being impregnated with a mixture of carbolic acid and melted bees-wax, and was kept in a five per cent. solution of carbolic acid until required. Catgut was also used in suitable cases for stitches, silver wire was employed where much tension existed, and silkworm gut and horsehair were utilized especially in septic cases. Later, waxed silk was replaced for most purposes by ordinary Chinese twist, rendered aseptic by having been steeped in 1 to 20 watery solution of carbolic acid.

It was at about this period also that Lister began to make use of the india-rubber drainage-tubes devised by Chassaignac early in the century for carrying off pus. Though no pus was formed in aseptic wounds, yet a considerable flow of blood and serum followed immediately upon the infliction of the wound, however

[1] Vol. ii, p. 119. [2] Vol. ii, p. 139.

managed. Pressure forceps, the use of which makes it possible to stanch by a few minutes' pressure, and, if thought necessary, to tie all bleeding-points, had not yet been introduced. Moreover, the stimulation of the wound by the antiseptic fluid, even though the endeavour was made to reduce this to a minimum, increased the flow of serum. To prevent the accumulation of these discharges, Lister had been in the habit of introducing and retaining for at least forty-eight hours, at one angle of the wound, a strip of lint soaked in a solution of carbolic acid and oil (1 to 4). The substitution of india-rubber drainage-tubes proved a valuable improvement in antiseptic technique. They were, of course, kept constantly immersed before use in a strong solution of carbolic acid.

Holding the view that the dust floating in the air was a potent source of infection, but recognising that the contact of carbolic lotion with the wound during the operation and at subsequent dressings was a source of irritation, Lister at about this period introduced the use of a spray of carbolic acid solution to play around the wound, with the view of destroying the germs floating in the air before they settled on the wound. He, however, eventually convinced himself, firstly, that the spray did not thoroughly disinfect the atmospheric dust, and secondly, that not only were the microbes in the air for the most part not pathogenic, but also that the tissues were capable of destroying organisms, provided they were neither very numerous nor very virulent. After full consideration of all the facts, and especially those constantly observed in the treatment of empyema,[1] Lister abandoned the use of the spray without reverting to the other precautions against the atmospheric infection which had formerly been deemed, and perhaps then were, essential.

Although carbolic acid had proved so conspicuously satisfactory as an antiseptic for use in surgery, it was open to two objections. The first was that it was irritating to the wound, and must therefore to some extent retard healing, and was poisonous if absorbed in quantity ; the second, that, being volatile, it was constantly being dissipated from the dressings, which it was therefore deemed advisable to change oftener than would otherwise have been necessary. Lister, consequently, was always seeking to find some substance which, while possessing adequate antiseptic properties, would yet be unirritating, non-poisonous, and non-volatile.

Among a large number of substances which were tested in practice, the following may be mentioned. In consequence of reports as to the value of boracic acid for the preservation of food, this substance was very extensively tried ; it was, however, found to be quite inefficient as an antiseptic for ordinary practice, but it did very well in the case of superficial sores and ulcers, and for

[1] Address to International Medical Congress, Berlin, 1890. Reprinted in vol. ii, p. 332.

those purposes it has continued to be used. At the present time, under suitable circumstances, boracic lotion (saturated solution of boracic acid in water), boracic lint, and boracic ointment are commonly employed. Salicylic acid was much praised by Thiersch, and was consequently carefully tested by Lister, but it was found to be open to many objections, especially that it was irritating to the wounds, and inefficient as an antiseptic. It is only used now in the form of salicylic wool and salicylic ointment. Thymol was for a time a favourite antiseptic with some surgeons, but after testing it in various ways it was rejected as being untrustworthy. Preparations of eucalyptus also failed to meet the requirements, and it only remains in use in the form of ointment, which is still occasionally employed, chiefly in the treatment of burns. Acetate of alumina was used to a considerable extent at one time, but on putting it to a careful test it also was rejected.

After the publication of Koch's earlier papers on disinfection, the various mercurial salts were examined, and they form a very essential part of the antiseptic equipment at the present time. A good deal of time was expended in testing the relative merits of lotions of the biniodide and perchloride of mercury; the conclusion reached was that, from every point of view, especially in respect to its efficiency as an antiseptic and lesser tendency to irritate the skin and the wound, the perchloride was superior to the biniodide. The strength of the perchloride lotions employed at an early period, 1–2000 and 1–4000, were the strengths used by Lister at the end of his work, and are still extensively employed. A great deal of labour was also expended on finding a suitable mercurial dressing which should, on the one hand, be non-irritating to the skin, and on the other would provide a sufficient store of antiseptic to obviate the necessity of frequent changing of dressings, even when the discharge was considerable. The record of several of these attempts will be found in the published papers; for example, we have[1] a description of an attempt to form a gauze with a combination of perchloride of mercury and albumen. This again, gave place[2] to a gauze containing the double chloride of mercury and ammonium (sal alembroth). Sal alembroth, however, had the defect of being very soluble in the serum of the discharges, and the solution so formed was very apt to irritate the skin; it eventually gave place to the double cyanide of mercury and zinc, which was quite unirritating, and while sufficiently soluble in blood to give to the gauze charged with it sufficient antiseptic power to inhibit the growth of microbes, was yet not so soluble as to be washed out of the dressing by the discharges, however copious. An aniline dye added to the salt was found to have the double advantage of fixing the double cyanide in the gauze, so that it did not shake out when

[1] Vol. ii, p. 303. [2] Vol. ii, p. [illegible].

dry, and of indicating that the dressing had been uniformly charged. The use of this insoluble and non-volatile antiseptic allowed the macintosh covering to be dispensed with, and thus the discharges could dry up and the gauze became a dry dressing. In place of macintosh, a mass of antiseptic wool (double cyanide or salicylic) was applied outside, so as to add to the thickness of the antiseptic material through which the discharge had to pass.

Lister, as Cameron has pointed out,[1] was probably the first to use a dressing sterilized by heat, and not containing any antiseptic substance. This he did while still Professor in Edinburgh, and the material used for the purpose was absorbent cotton-wool. He did not, however, persevere in the practice, because he felt that it could only be safely adopted in such cases as furnished a comparatively small amount of discharge, for if the discharge came through the dressing without having acquired any antiseptic material in its passage, there was nothing to prevent putrefaction spreading into the wound. Hence in cases in which there was a considerable amount of discharge, it was necessary to change the dressings very frequently; and further, the successful employment of sterilized materials not containing antiseptics was a much more difficult and complicated matter than the use of antiseptic dressings, and implied considerable practical experience in bacteriological work. He therefore preferred to retain the use of antiseptics judiciously chosen and carefully used, so that, while their germicidal influence was retained, an irritating effect was avoided.

By the time he ceased active work as a surgeon, he had arrived at a method of wound treatment in which the maximum amount of protection against bacterial invasion was secured with a minimum amount of irritation to the wound. The result was that the frequent dressings formerly employed were given up, and usually one dressing, or at most two, sufficed for a clean case. At the same time also the irritation of the wound had been so much reduced that, in a great majority of cases, there was no necessity for drainage; in fact, his ideal of a subcutaneous injury had been more or less attained.

GENERAL SURGICAL ACTIVITY

Apart from the surgical improvements directly resulting from the prevention of sepsis, Lister published various articles on other surgical subjects. Attention may especially be directed to the article on excision of the wrist,[2] and to the essays on amputation and anaesthetics[3] written for *Holmes's System of Surgery*. The article on amputation differs from other articles on the same subject written at that date, in that it presents the reader with the principles

[1] loc. cit. [2] Vol. ii, p. 417. [3] Vol. ii, p. 378; vol. i, p. 135.

which should guide the surgeon in dealing with the several parts of each limb, and omits those tedious details which are often more confusing than instructive. One of the best amputations of the thigh is here described for the first time. The essay on anaesthetics set forth the methods then employed in Edinburgh, and supported them by scientific arguments in favour of their validity. The subject of anaesthetics was one in which Lister has always taken the keenest interest, and it is needless to add that his teaching has many followers at the present day.

Another very interesting paper was that on the effects of the position of a part on the circulation through it.[1] For years before the introduction of Esmarch's bandage, Lister had been in the habit, in operations on the extremities, of elevating the limb for a few minutes, and then, while it was still elevated, applying a tourniquet at the upper part; in this way he brought about a bloodless state of the limb. On the publication of Esmarch's paper, Lister adopted his elastic band in place of the tourniquet; but he continued to employ elevation of the limb, as a safer means of emptying it of blood in the first instance than the application of a bandage from below upwards, as advised by Esmarch. In the paper to which reference is made Lister explained his views as to the mode in which his plan brought about the desired exsanguine state.

As soon as it became evident that antiseptic methods protected the patient against septic diseases, a great change came over general surgical treatment, and from the very first there was not a case admitted into Lister's wards which was not considered from a fresh point of view. The dangers arising from the risk of wound infection being averted, the question arose in most instances whether something better might not be done in the way of treatment by operation than had been customary. The result of the treatment of compound fractures by the antiseptic principle was that instead of looking on amputation of the limb as an imperative procedure, in the great majority of cases that plan became relegated to a secondary place, and all the surgeon's energies were devoted to an attempt to save the limb. The result is that nowadays amputation is only very rarely performed in compound fracture, or compound dislocation. The method led also to a complete revolution in the treatment of spinal abscess and tuberculous abscesses of joints generally. Quite early the subject of ununited fractures was taken up, and instead of employing apparatus or inefficient subcutaneous operations, the bones were boldly cut down upon and repaired in any way which seemed mechanically advisable. From that it was but a step to operations on recent fractures,—the patella, for example—to operations for malunited fractures, and to osteotomy for knock-knee and other deformities.

[1] Vol. i, p. 176.

Operations on healthy and diseased joints were introduced—the bold removal of loose bodies from joints, drainage of chronic synovitis, incision into diseased joints, and so on. Extensive operations for cancer of the breast became justifiable, and his results as regards recurrence in those early days were very excellent. Were it necessary, it would be easy to enumerate many improvements and fresh operations which were carried out by him from the very first. Indeed much of the present operative work was directly initiated by Lister, although he published very little with regard to it, for as such innovations seemed to follow naturally from the altered course of wounds, Lister did not consider that the publication of improvements in individual operations was necessary. The great charm of Lister's hospital work and lectures in the early days was not only the way in which the wounds healed, and in which the patients operated on recovered without pain, or fever, or illness, but also the fresh point of view from which every surgical affection was considered, and the manner in which the ancient canons of surgical practice were one by one overthrown.

PART I. PHYSIOLOGY

OBSERVATIONS ON THE CONTRACTILE TISSUE OF THE IRIS

[*Quarterly Journal of Microscopical Science*, vol. i (1853), p. 8.]

OUR knowledge of the cause of the movements of the iris was till within the last few years in a very unsatisfactory condition. That this organ possessed contractile fibres was a matter of inference, not of direct observation. In the third part of the last edition of Quain's *Anatomy*, published in 1848, we find it stated (p. 915) that the radiating and circular fibres of the iris are generally admitted to be muscular in their nature, but the grounds for that admission are not mentioned. Mr. Bowman's Lectures on the Eye, delivered in the summer of 1847, and published in 1849, show us that the then state of histology in this country did not enable that accomplished microscopical anatomist to identify the fibres of the iris with other plain (unstriped) muscular tissue. At p. 49 he says, 'The fibres which make up the proper substance of the iris are of a peculiar kind, very nearly allied to the ordinary unstriped muscle, but not by any means identical with it.' He afterwards goes on to argue that, as we know that the organ changes its form, and as its vessels are so distributed that it cannot be erectile, we have no other resource than to consider its fibres contractile, which conclusion he supports by reference to the striped fibres in the iris of birds and reptiles.

In 1848 Professor Kölliker announced to the world his grand discovery of the cellular constitution of all plain muscular tissue, in a full and elaborate paper in the *Zeitschrift für wissenschaftliche Zoologie*.[1] At p. 54 of the first part of the first volume of this journal, after speaking of the arrangement of the

[1] Professor Kölliker may almost be said to have been anticipated in this discovery by Mr. Wharton Jones. Through the kindness of that gentleman, I have now before me two original drawings, made by him about the year 1843, of plain muscular tissue from the small intestine. In one of these the muscular fibre-cells are characteristically shown, except that their nuclei are not apparent; one of them is wholly isolated. In the other drawing, the alternate disposition of the fibre-cells is seen after the addition of acetic acid. He also observed, as he informs me, that the unstriped muscle of the oesophagus and stomach, and also of the uterus and other organs, consisted of similar elements—a fact which he yearly communicated to his class in his public lectures at Charing Cross Hospital. He was led, from appearances in the embryo, to infer that striped muscular fibre is originally composed of similar elements, which, in the process of development, are enclosed in a sarcolemma common to many of them, and become split into fibrillae. He thus accounted for the nuclei of striped muscular fibre, which, according to this view, are the persistent nuclei of the primitive muscular fibre-cells.—J. L.

fibres of the ciliary muscle, the sphincter pupillae, and dilator pupillae, he makes the following statement: 'The elements of all these muscles are undoubtedly smooth muscular fibres. In man I have but seldom succeeded in isolating the individual fibre-cells, but I have had more frequent success in the case of the sheep, where I found them in the ciliary muscle, on an average, 1-600th of an inch in length, and 1-4000th to 1-3000th of an inch in breadth. In man, in all these muscles one sees, as a rule, only parallel fibres projecting to a greater or less extent at the edges of small fragments of the tissue, these fibres exhibiting in abundance the well-known elongated nuclei, either with or without the aid of acetic acid. In man, the muscle of the choroid (ciliary muscle) has broader and more granular fibres and shorter nuclei than the iris. In the former the nuclei measure from 1-2400th of an inch to 1-1333rd of an inch; in the latter as much as 1-1090th of an inch.'

Here, then, we have, so far as I know, the first and only recorded observation of tissue in the iris identical with ordinary unstriped muscle.

It is to be remarked that, where he alludes, in the passage above quoted, to having in rare cases separated the individual fibre-cells of the muscular tissue, Professor Kölliker speaks of the three muscles (ciliaris, sphincter, and dilator) collectively; in other words, that he does not tell us in plain terms that he has isolated the fibre-cells of the iris at all. Now, the ciliary muscle is confessedly easier to deal with than the iris. Mr. Bowman, who speaks so doubtfully of the fibres of the iris, says of the ciliary muscle, 'the fibres are seen to be loaded with roundish or oval nuclei, often precisely similar to those of the best marked examples of unstriped muscle' (op. cit., p. 53). Another very eminent microscopical anatomist has informed me, as the result of his experience, that it was easy to identify the tissue of the ciliary muscle with that of other organic muscle, but that this had not been the case with the iris. That Professor Kölliker's isolation of the fibre-cells of the muscles of the eye was in reality confined to the ciliary muscle is rendered probable by the fact that, while the whole article quoted from shows a manifest desire on the part of its author to give all available detail, yet regarding the iris he mentions no facts requiring isolation of the fibre-cells for their determination; while, on the other hand, he tells us that the fibre-cells of the iris are narrower than those of the ciliary muscle, and gives the length of the nuclei in the human iris—things which are very readily observed without isolation of the fibre-cells. His figures refer to the human ciliary muscle alone; and the only measurements given by him of muscular fibre-cells from the eye refer to the same muscle in the sheep.

It would seem, then, that with regard to the iris, Kölliker's proof falls short of the test of isolation of the fibre-cells.

An operation for artificial pupil, by excision, performed by Mr. Wharton Jones, at University College Hospital, on the 11th of August of the present year (1852), placed in my possession a perfectly fresh portion of a human iris, and, without knowing that Kölliker's observations had extended to the muscles of the eye, I proceeded to avail myself of this somewhat rare opportunity of investigating the muscular tissue of the human iris. On placing under the microscope, four hours after the operation, portions of the tissue carefully teased out in water with needles, I found that some of the muscular fibre-cells had become isolated, and presented very characteristic appearances. I accordingly made camera-lucida sketches of the finest specimens, which are reproduced on a smaller scale in the accompanying figures (see Pl. I, A, Figs. 7–11). I drew the last cell (Fig. 8) nine and a half hours after the operation. And here I may mention that I have not found the muscular fibre-cells by any means a very perishable tissue. After an iris has been soaking two or three days in water, the muscular tissue of the sphincter is still quite recognisable, not only by the nuclei, but also by the individual fibre-cells.

Of the figures above referred to, (7) and (8) are examples of the most elongated cells that I saw. By reference to the scale it will be found that the cell (7) is about 1-125th of an inch in length, and about 1-3750th of an inch in greatest breadth ; while (8) is a little shorter, but of about the same average breadth. Kölliker divides muscular fibre-cells into three artificial divisions, according to their shape, of which the third contains the most elongated and most characteristic cells. Of this third division, the cells (7) and (8) are good examples, and, in fact, correspond in their measurements to average fibre-cells of the muscular coats of the intestines. The cells (9) and (10), though less characteristic in respect of their length—(9) being about 1-333rd of an inch in length, and 1-3000th of an inch in breadth, and (10) 1-300th of an inch by 1-3000th of an inch—yet present the same peculiar delicate appearance and soft outline, and the same elongated nucleus, of not very high refractive power relatively to the contents of the cell, but clearly defined. All these cells have the same flat or ribbon-like form which is exhibited by the cell (8) at *a*, where one edge has become turned up by a folding of the cell ; at *b* there seemed a tendency to transverse arrangement of the granules of this cell, which tendency is more strikingly exhibited at *b* and *c* in the cell (11), which, though not isolated, is introduced on that account. This tendency to transverse arrangement of the granules was long since noticed by Mr. Wharton Jones, as that gentleman has since informed me, and is, indeed, indicated in the drawings which are alluded to in the note above. In the cells of this iris, however, it was not by any means constant. Some of them, as (7) at *a*, and (9) at *a* and *b*, exhibited something of a longitudinal arrangement of the granules, such as was noticed some years since in unstriped muscle by Mr. Bowman, who considered the rows of granules as an approach to the fibrillae of striped muscle. These cells are more granular than I have found those of the iris of the horse to be; but I may here mention that, on comparing with these drawings the outline of a fine specimen of a muscular fibre-cell of the sphincter pupillae of this animal, which I had sketched by the camera lucida, I find it to be almost an exact counterpart of the cell (7) as regards the shape and size of both the cell and its nucleus. The nuclei of these cells measure from 1-1400th to 1-1110th of an inch in length, and about 1-9500th of an inch in breadth. They are not, however, the most characteristic that are to be found in the iris. Fig. 12 is from a camera-lucida sketch of a nucleus of the sphincter pupillae of a horse; it measures 1-840th by 1-15200th of an inch, and exhibits in a very marked manner the true rod-shaped figure which appears peculiar to muscular fibre-cells. On the other hand, I found some instances in the human iris of fibre-cells with considerably broader nuclei than those in the figures. The iris that yielded these cells was a blue one, apparently perfectly healthy; it was active and brilliant before the operation, which was performed on account of central opacity of the cornea, resulting from an attack of a severe form of ophthalmia fifteen months previously. I watched the case closely from the first, and there was no reason to suspect implication of the iris in the inflammation.

Having thus satisfactorily verified the fact of the existence in the iris of tissue identical with ordinary unstriped muscle, I was naturally led to inquire into its distribution in the organ: and, as this is a subject of great interest, and one about which much difference of opinion has prevailed, I may mention here the facts which I have hitherto observed, although there be not very much of actual novelty in them.

Kölliker, in the article above referred to (loc. cit., pp. 53 and 54), describes a sphincter and dilator pupillae, the former 'very readily seen in the white rabbit, or the blue iris of a man, from which the uvea has been removed, about a quarter of a line broad in man, exactly forming the pupillary margin, and situated somewhat nearer the posterior surface of the iris'. Of the dilator he says, while confessing the difficulty of the investigation, that he believes it to consist of many narrow bundles, which run inwards separately between the vessels, and are inserted into the border of the sphincter.

Bowman, on the other hand, states (op. cit., p. 48) that, while in some instances a delicate narrow band of circular fibres exists at the very verge of the pupil, yet, in the majority of instances, he feels *sure* that no such constrictor fibres of the pupil exist. He ascribes the contraction of the pupil to the inner part of the radiating fibres, which, he says, are joined and knotted in a plexiform manner round the pupil. It is scarcely needful to observe that such a statement from such an authority could not but go far to impugn Professor Kölliker's assertion respecting the existence of a sphincter pupillae.

My experience, I must confess, accords with that of Kölliker, viz. that the sphincter is readily seen, while the dilator is that whose investigation alone presents very serious difficulty. In the first iris that I examined with a view to the distribution of the muscular tissue, I was struck, after removing the uveal pigment, with the appearance of a band on the posterior surface of the iris, near the pupil and parallel to its margin, quite evident to the naked eye, elastic and highly extensible. This proved to be the thickest part of the sphincter pupillae. I have examined six human irides with reference to the distribution of the muscular tissue, but in none have I had any difficulty in recognizing the sphincter, which I have also found equally distinct in some of the lower animals, viz. in the rabbit, the guinea-pig, and the horse. In man I find it about 1-30th of an inch in width, thickest towards its outer part, where it lies nearer the posterior surface of the iris than the anterior, and thinning off towards the pupil, where it forms a sharp margin, covered apparently on its anterior aspect only by some vessels and nervous threads and a delicate epitheliated membrane, which is thrown into beautiful folds when the pupil is contracted. The fibres of the sphincter are not absolutely parallel, and this deviation is probably produced in part by the dilating fasciculi sweeping in at various parts in a curved manner, and becoming blended with the sphincter. The reason for this supposition will appear hereafter. By teasing out under the microscope a portion of the actual pupillary margin, I found the sphincter to consist at this part of apparently unmixed muscular fibre-cells, without any connecting cellular tissue. Fig. 13 is a camera-lucida outline of the edge of a portion of the sphincter so prepared, which edge is seen to be formed of projecting fibre-cells, and similar appearances may be seen with great readiness under a high power, after stroking the pupillary margin with the point of a needle. Indeed, the great facility with which the tissue may be thus broken up appears opposed to the idea of the fibre-cells being united end to end into fibres, as the descriptions formerly given of unstriped muscle would lead one to suppose. The ends appear to separate as readily as the edges and surfaces, and it would rather seem as if the fibre-cells of a fasciculus were placed with their long axis in one direction, cohering generally to one another, but without the formation of longer fibres than each cell itself constitutes. I may here mention incidentally that in the circular coat of the aorta of the sheep, where the muscular tissue is disposed in thin layers among the elastic tissue, I have observed a distinctly alternate arrangement of the fibre-cells without any formation of fibres. Mr. Wharton Jones's drawing of alternately disposed fibre-cells in the small intestine has been alluded to in the note above. A portion of the outer and thicker part of the human sphincter pupillae proved also extremely rich in muscular fibre-cells. In the rabbit and guinea-pig the sphincter has much the same appearance as in man, whereas in the horse it forms a wide but very flat band.

The dilating fibres of the iris present a very difficult subject of investigation.

And here I must express my belief—a belief the result of repeated and very careful observations—that the fibres described by Mr. Bowman as probably the contractile fibres of the iris are in reality the outer cellular coats of the vessels. The outer coat is very abundant in the vessels of the iris, and indeed even in the blue eye towards the sphincter quite obscures the bore of many of the vessels, and prevents the recognition of their vascular character, which can only be determined by tracing them to their more external and more obvious vascular trunks. The distribution of these vessels, radiating between the sphincter and the circumference of the iris, and forming in the region of the sphincter a close and knotted plexus, corresponds accurately with Mr. Bowman's description of the distribution of the fibres of the iris. His account of the tissue of these fibres, which he considers as probably contractile, harmonizes with the characters of the cellular tissue that clothes the vessels. This is peculiar ; consisting of very soft looking fibres, whose fasciculi often require the best aid of a first-rate glass to resolve them into their constituent elements ; destitute apparently of yellow elastic fibres, as in the case of the cellular tissue of the uterus, but, like this, containing abundance of free nuclei, of roundish or elongated form. The fibres are completely gelatinized by acetic acid. Now such a tissue can hardly, in the present state of our knowledge, be regarded as contractile ; at any rate, if we can find any ordinary muscular tissue to account for the dilating action. On teasing out portions of the outer part of the human iris, I have found long delicate fasciculi, whose faint outline, absence of fibrous character, and possession of well-marked elongated nuclei parallel to the direction of the fasciculus, left no doubt in my mind that they were plain muscular tissue.

So far my observations regarding the dilator agree with Kölliker's, but whether or not these fasciculi are connected with the cellular coat of the vessels I have hitherto been unable to determine.

Among the lower animals the albino rabbit and guinea-pig appeared but little suited for the elucidation of this point. I have been most successful with the eyes of a horse, where, from the thickness of the iris and the abundance of pigment (for the eyes were black ones), I anticipated but little result from my examination. Having removed the uveal pigment from behind, I found that I was also able to strip off from the anterior surface a tough membrane, a portion of which, put under the microscope, appeared to be made up of peculiar short felt-like fibres, which were gelatinized by acetic acid. At and near the pupillary margin this membrane comes off in a continuous layer, leaving a delicate reticular structure, which contains the muscular tissue. It also contains vessels, as I proved by injection, and a black network, which consists of fine fibres, yellow, and highly refracting, more or less encrusted with pigment. I am uncertain whether or not this be a network of divided nerve-tubes with adhering pigment ; in some spots the pigmental crust was absent from a considerable length of the fibres. The sphincter pupillae is beautifully seen as a broad flat band, of extremely well-marked, unmixed, muscular fibre-cells ; but crossing this at right angles are found, here and there, other flat bands of fibre-cells, which are in so thin a layer that without isolation the width of the individual cells can be seen, and they are evidently of similar dimensions to those of the sphincter. On addition of acetic acid their nuclei are also seen to be exactly like those of the sphincter. These bands divide in their course towards the pupil into several fasciculi, some of which cross over the sphincter at right angles till very near to its pupillary margin, and then seem to blend with the sphincter by making a slight curve. Most of the fasciculi, however, arch away earlier from their first course and join the sphincter in more or less oblique lines. The bands from which these fasciculi diverge may be traced away from the pupil for some distance, continuing their course at right angles to the sphincter till they are obscured by other tissues. Hence I think the inference may fairly be drawn that these are the insertions of the dilating muscular bundles. In the horse, then, the dilating fasciculi appear to consist of precisely the same tissue as the sphincter, and to blend with it in their insertion. The flat bands of muscular tissue above spoken of seemed to have no special relation to the vessels, some of which were filled with injection. In the outer part of the iris of the same horse I found a delicate muscular fasciculus lying near but not intimately connected with one of the radiating vessels of this part. In the human iris I have seen a muscular fasciculus, as it appeared from the nuclei it contained, crossing the sphincter at right angles for a short distance ; this observation, so far as it goes, seems to imply that the same mode of insertion of the dilator occurs in man as in the horse.

The fibre-cells of the dilator appear to be held together much more closely than those of the sphincter, at least in the outer part of the iris ; for I have never been able to define the individual fibre-cells in a perfectly satisfactory manner in the dilator, though I have often teased out portions of the outer part of the iris. The dilating muscular tissue is also probably less abundant than the muscular tissue of the sphincter ; and this, if the fact, will help to account for the comparative difficulty in discovering it. I may here mention that both in the cat and in the rabbit, soon after death, dilatation of the pupils being present, exposure of one iris to the air caused it to contract at once, while the pupil continued dilated in the other eye, which was untouched. I do not know if this fact has been observed before, but it is interesting in two ways —first, as showing that the muscular tissue of the iris, like other muscular tissue, is obedient to the stimulus of exposure ; and, second, as proving either that the sphincter is in these animals a decidedly more powerful muscle than the dilator, which is equally exposed to the stimulus ; or else that the fibres of these two muscles have different endowments, as has been shown by Mr. Wharton Jones to be the case with the muscular tissue of the arteries and veins of the bat's wing ; where, although the veins are muscular, and even contract rhythmically, yet the arteries alone exhibit tonic contraction when irritated by mechanical stimulus.

A rich network of extremely fine fibres, seen readily in the blue human iris viewed from the anterior aspect, appears to represent the nerves of the organ. The fibres are of a yellowish colour, and are possessed of pretty high refractive power ; they present, if really nervous, a good illustration of the division and anastomosis of ultimate nerve-fibres ; the smallest divisions visible under a high power are seen only as fine lines.

I have not seen any nerves in the human iris presenting the double contour ; but in the iris of a cat, so fresh that the tissue contracted under the needles as I teased it out, the double contour of the nerve-tubes was already very strongly marked, showing the existence in this animal of the white substance of Schwann in these nerves. The double contour surrounded the ends of the nerve-fibres which I supposed to have been broken by the teasing process. This last fact seemed to confirm the general belief that the double contour is a post mortem effect, which, however, was in this instance a very rapid one.

I believe that a further investigation of the fresh blue iris in man, and of the horse's iris, would supply the means of finally settling the question of the distribution of the dilator pupillae.

My engagements do not allow me to carry the inquiry further at present ; and my apology for offering the results of an incomplete investigation is, that a contribution tending, in however small a degree, to extend our acquaintance with so important an organ as the eye, or to verify observations that may be thought doubtful, may probably be of interest to the physiologist.

OBSERVATIONS ON THE MUSCULAR TISSUE OF THE SKIN

[*Quarterly Journal of Microscopical Science*, vol. i (1853), p. 262.]

AMONG the abundant new matter contained in those parts of Kölliker's *Mikroskopische Anatomie* that are hitherto published, there is perhaps nothing more striking than the announcement that small bundles of unstriped muscle exist in all parts of the dermis that are provided with hairs, connected inferiorly with the hair-follicles, just below the sebaceous glands, and passing up obliquely towards the free surface of the skin.

The effect of the contraction of such little muscles must necessarily be to thrust up the hair-follicles and depress the intermediate portions of skin ; in other words, to produce cutis anserina ; and thus this condition, previously quite unaccounted for, received at the hands of Professor Kölliker a simple and beautiful explanation.

In March of the present year (1853) I made an attempt to verify this most interesting discovery ; and although the somewhat arduous duties of a resident office in University College Hospital prevented me from making the investigation as extensive as I could have wished, yet I found myself able not only to verify, but in some slight degree to add to Kölliker's observations. And as the main fact of the muscularity of the skin had not previously, so far as I am aware, found confirmation in this country, I have been induced to publish my results in the hope that they may prove acceptable to the microscopical anatomist.

Kölliker originally described[1] these muscles of the skin as flat bundles of unstriped muscular tissue, from 1-120th of an inch to 1-75th of an inch in breadth, of which there appeared to be one or two in connexion with each hair-follicle : it seemed probable to him that they arose from the superficial parts of the corium, and he had clearly seen them passing obliquely downwards to their insertion into the hair-follicles, close behind the sebaceous glands which they embraced. In his *Handbuch der Gewebelehre*,[2] published in 1852, he gives in the text exactly the same account of these muscles, except that he no longer expresses any doubt regarding their origin from the superficial parts of the corium. He afterwards states in a note that these muscles had been very

[1] Vide *Mikroskopische Anatomie*, vol. ii, part i, p. 14.

[2] Vide *Handbuch der Gewebelehre des Menschen*, p. 82.

recently seen by two observers, Eylandt and Henle, both of whom, however, had found them narrower than he. Eylandt, who named them '*arrectores pili*', had never seen more than one bundle connected with each hair-follicle, and had failed to detect muscular tissue in the nipple and areola, and in the subcutaneous cellular tissue of the scrotum, penis, and perineum, where Kölliker had described it as existing. Henle had traced the muscles to the most superficial parts of the dermis, where they divided into numerous little bundles 1-3000th of an inch in diameter, which could be followed to immediately beneath the epidermis; he had also seen muscular tissue in the nipple, areola, and the other parts where Kölliker had described it, but, on the other hand, in the opinion of Kölliker, he had gone too far, inasmuch as he described bundles of plain muscular tissue as existing on the exterior of the sudoriferous glands and blood-vessels of parts destitute of hairs (such as the palm and sole). These Kölliker is unable to discover, and he believes that Henle has been misled by the use of boiled preparations, in which, as Henle himself states, fine branches of nerves are liable to be mistaken for muscle. Thus it appears that the confirmation furnished by these two observers is by no means a very satisfactory one, and that Henle, the only authority on whom we rest for the fact of the muscles taking origin immediately beneath the epidermis, cannot, in the opinion of Kölliker, be implicitly relied on with reference to this investigation. It appears remarkable that Eylandt should have failed to discover muscular tissue in the scrotum, for the dartos was long since proved to owe its contractility to unstriped muscle. Of the parts in question I have examined only the areola mammae, which, however, answered well to the description given by Kölliker, who states[1] that the bundles of muscle are there circularly disposed, forming a delicate layer in the deeper parts of the corium, and encroaching slightly on the subcutaneous cellular tissue. On dissecting a portion of an areola from the subcutaneous tissue towards the surface, I found on reaching the deepest part of the dermis a delicate reddish-yellow fasciculus circularly arranged; and a portion of this, teased out with needles, and treated with acetic acid, presented in a well-marked manner the nuclei of plain muscular tissue. A camera-lucida sketch of a small portion is given on a reduced scale in Pl. I, B, Fig. 6.

In enumerating the parts where he has met with muscles connected with the hairs, Kölliker does not mention the scalp, probably because the density of the tissue of this part rendered it unfit for investigation by the method in which he prepared his objects, viz. isolating a hair-follicle with its sebaceous glands and treating it with acetic acid. Its very firmness and consistence,

[1] Vide *Mikroskopische Anatomie*, vol. ii, part i, p. 14.

however, make the scalp better adapted for fine sections than any other part of the skin ; and as I succeeded better with sections than by the other method, the scalp has received most of my attention. By compressing a portion between two thin pieces of deal, and cutting off with a sharp razor fine shavings of the wood and scalp together, moderately thin slices may be obtained. Fig. 4 represents a perpendicular section made in this way, and treated with acetic acid ; the epithelium has become detached from the free surface *a*, *b* ; *b*, *c* is part of one of the muscles near its superficial attachment, and it illustrates pretty well the appearance presented by them under a rather low power. They are distinguished from the tissue around them by their transparent and soft aspect, and by the abundant elongated nuclei scattered through them. Under a higher power the characteristic 'rod-shaped' nuclei become fully brought out, and no doubt remains as to the nature of the tissue. A good example of nuclei so magnified, derived from a muscle connected with a hair-follicle of the pubes, is shown in Fig. 5. It will be observed in Fig. 4 that the muscle has been traced to within a very short distance of the surface, where the nuclei became obscured by other tissues.

But I afterwards found that much better sections could be obtained from dried specimens. A portion of shaved scalp being placed between the two thin slips of deal, a piece of string is tied round them so as to exercise a slight degree of compression ; the preparation is now laid aside for about twenty-four hours, when it is found to have dried to an almost horny condition. It then adheres firmly by its lower surface to one of the slips, and thus it can be held securely, while extremely thin and equable sections are cut with great facility in any plane that may be desired. These sections, when moistened with a drop of water and treated with acetic acid, are as well suited for the investigation of the muscular tissue, as if they had not been dried.

Fig. 1 is slightly reduced from a camera-lucida sketch[1] of such a section, made in a plane perpendicular to the surface of the scalp, and at the same time parallel to the sloping hairs. I find that such a plane always contains the muscles in their entire length, the reason of which will appear shortly. In this figure *d* is the corneous, and *e* the mucous layer of the epithelium ; *b*, *b* . . . are the hair-follicles with their contained hairs, both have been more or less mutilated by the process of section ; the second hair from the right being a short one, its bulk is seen : *c*, *c* . . . are the sebaceous follicles, also more or less mutilated : a_1, a_2 . . . a_6 are the muscles, which appear, under this very low power, merely as transparent streaks, and require a higher power to make out their tissue.

[1] In all the sketches from which the figures that illustrate this paper have been taken, I have used the camera lucida, which instrument has the great advantage of ensuring correctness of proportions.

The muscles are seen to arise in all cases from the most superficial part of the corium, and to pass down obliquely to their insertions into the hair-follicles immediately below the sebaceous glands. It will be remarked that the muscles are here all on the same side of the respective hair-follicles, viz. on that side towards which the hair slopes: and such I found in the examination of a large number of sections to be always the case. This is an interesting fact, as such an arrangement of the muscles is exactly that which is best adapted for erecting as well as protruding the hairs, which must be drawn by their contraction nearer to the perpendicular direction. That this erection as well as protrusion of the hairs does occur, I have proved by artificially exciting the state of cutis anserina upon my own arm and leg. Tickling a neighbouring part will often induce horripilation, and if the eye is kept on an individual hair at this time, it is seen to rise quickly as the skin becomes rough, and to fall again as the horripilation subsides. I have never seen more than one muscle to each hair-follicle in the scalp; and in order that a single muscle may by its contraction simply erect a hair, it must be placed in a plane perpendicular to the surface of the skin and parallel to the hair; this explains the fact before alluded to, that a section made in such a plane is sure to contain the muscles in their entire length if at all, while sections in other planes cut across either the muscles or the hairs.

Fig. 2 represents the superficial attachments of the two muscles a_1 and a_2 of Fig. 1; *a* being the upper end of a_1, and *b* that of a_2; *c* is the corneous, and *d* the mucous layer of the epidermis; the intervening tissue between the muscles was omitted in the sketch to save time. *b* furnishes a good example of the subdivision of a muscle into secondary bundles near the surface, as observed by Henle, while in *a* the subdivision, if it has occurred at all, is certainly not carried so far: the muscle *b c* in Fig. 4 seems not to have undergone any subdivision: in some cases a simple bifurcation of a muscle near the surface is all that is seen: hence the splitting up of the muscles into smaller bundles near their upper attachment appears not to be a constant thing, and when it does occur, exists to a very variable degree in different muscles. Want of room in the plate has rendered necessary so great a reduction of the scale[1] from the original drawing, as barely to allow the nuclei of the muscles to be perceived; by looking closely, however, it may be seen that at *e* and *f* nuclei exist immediately under the epithelium, and before introducing them into the sketch, I ascertained, by a higher power, that they were really of the same character as those in other parts of the muscles. At *g* it was impossible to trace the nuclei so far; if any existed here, they were obscured by the fibrous

[1] Figs. 2, 3, and 4 have all been reduced one-half from the original sketches.

tissue of the scalp, which adheres to the muscles throughout their whole length, but appears to form special sheaths for the bundles of origin at the surface, and these sheaths interfere considerably with the examination of the muscular tissue enclosed by them. In some cases, however, they seem to be prolonged beyond the point to which the muscular tissue reaches, acting as tendons of attachment, and this may perhaps be the case at *g*: I have seen one striking instance of this mode of attachment, where a muscle having divided into two portions at some depth below the surface, a pretty long band extended like a cord to the surface from one of the divisions, and acetic acid having been added, nothing whatever but yellow elastic fibres could be seen in this band (the white fibres had been of course gelatinized). As a general rule, however, the muscular tissue extends to within a very short distance of the epithelium, and often, as above stated, can be detected immediately beneath it, as Henle has represented.

In Fig. 3 is shown the connexion of the muscle a_1, of Fig. 1, with its hair-follicle ; so that were the muscle *a* of Fig. 2 continued far enough downward, it would join with *a* of Fig. 3. The hair and its follicle are seen cut across very obliquely : *b* is the hair, tilted somewhat out of its natural position in the inner root-sheath *c* ; *d* is the outer root-sheath (corresponding to the mucous layer of the epidermis), whose outer cells are perpendicular to the hair-follicle ; *e* is the 'structureless layer' of the hair-follicle ; *f* is the circular layer of Kölliker ; *g* the external longitudinal layer with which the muscle is seen to become blended. Several elongated nuclei appeared at g_1 ; whether these are derived from the muscle, which is evidently inserted a good deal into the part of the follicle that is hidden from view, or whether they are only the elongated nuclei that occur in all parts of the longitudinal layer of the follicle, is doubtful : their well-marked elongated character inclined me rather to the former opinion ; *h* is a part of one of the sebaceous follicles, which appears to have no special connexion with the muscle that simply passes close by it without embracing it, as Kölliker implies, or sending any muscular expansion over it ; and the same occurs in all cases, so far as I have seen ; *i* is a portion of the fibrous tissue of the dermis, showing its connexion with the surface of the muscle.

Kölliker's description of the muscles of the skin (see above, p. 9) does not quite accord with what I have seen in the scalp, either as regards their shape or size. The muscles in this part had not, in sections parallel to their course, the appearance of flatness ; and by cutting slices in the way above indicated, at right angles to their known direction, their transverse sections were readily seen, and proved to be often quite circular, sometimes somewhat elliptical or polygonal, showing their form to be that of more or less rounded bundles. Their average diameter is, according to my experience, 1-200th of an inch, which is less than half the average of Kölliker's measurements, but this discrepancy is probably due to difference of situation in the parts observed, Kölliker not having examined the scalp : for one muscle which I sketched from the pubes was very nearly 1-100th of an inch in diameter.

With regard to the statement of Henle, that muscular tissue exists in parts destitute of hairs, I have searched with diligence many good sections of both the palm and the sole, without having been able to discover any evidence of it on the exterior of either the sudoriferous glands or blood-vessels of these parts. In a section treated with acetic acid, the elongated nuclei of the internal coat of a small blood-vessel sometimes give it an appearance that might at first sight be mistaken for that of unstriped muscle ; but this is an error easily avoided by care, and I cannot but agree with Kölliker in thinking that, in some way or other, his boiled preparations have led Henle into error.

In order to verify Kölliker's statement [1] that no unstriped muscle exists in connexion with the vibrissae of mammalia, I examined the feelers of a cat. These large hairs extend far down into the tissues beneath the skin, and have a more complex muscular apparatus than the small hairs of the human skin. Bundles of muscles extend from the lower part of the gigantic hair-follicle obliquely upwards to the inferior aspect of the skin, and, in addition to these, there is muscle surrounding the large nerve that enters the base of each hair-follicle. These muscles were all of the striped kind, but extremely soft and extensile, and among the fibres were a number of very elongated nuclei, but I saw no distinct evidence of the admixture of unstriped muscle.

In conclusion, I may state that this investigation has proved to me the general correctness of Kölliker's original observations, and also of the results of Henle's further inquiry, except in the case of the alleged muscularity of parts destitute of hairs ; and I shall be happy if the little additional matter communicated in this paper shall be found to bear as well the scrutiny of others.

University College Hospital, June 1, 1853.

[1] Vide *Mikroskopische Anatomie*, vol. ii, part i, p. 15.

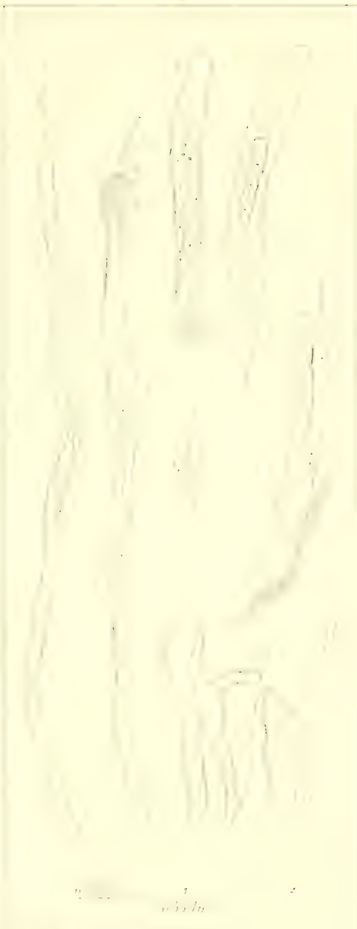


Fig 3

ON THE MINUTE STRUCTURE OF INVOLUNTARY MUSCULAR FIBRE

[*Transactions of the Royal Society of Edinburgh*, vol. xxi, Part IV (1857), p. 549.]

Read December 1, 1856.

It has been long known that contractile tissue presents itself in the human body in two forms, one composed of fibres of considerable magnitude, and therefore readily visible under a low magnifying power, and marked very characteristically with transverse lines at short intervals, the other consisting of fibres much more minute, of exceedingly soft and delicate aspect, and destitute of transverse striae. The former variety constitutes the muscles of the limbs, and of all parts whose movements are under the dominion of the will; while the latter forms the contractile element of organs, such as the intestines, which are placed beyond the control of volition. There are, however, some exceptions to this general rule, the principal of which is the heart, whose fibres are a variety of the striped kind.

Till within a recent period the fibres of unstriped or involuntary muscle were believed to be somewhat flattened bands of uniform width and indefinite length, marked here and there with roundish or elongated nuclei; but in the year 1847, Professor Kölliker of Würzburg announced that the tissue was resolvable into simple elements, which he regarded as elongated cells, each of somewhat flattened form, with more or less tapering extremities, and presenting at its central part one of the nuclei above mentioned. These 'contractile' or 'muscular fibre-cells', as he termed them, were placed in parallel juxtaposition in the tissue, adhering to each other, as he supposed, by means of some viscid connecting substance. In the following year the same distinguished anatomist gave a fuller account of his discovery in the first volume of the *Zeitschrift für wissenschaftliche Zoologie*, and described in a most elaborate manner the appearances which the tissue presented in all parts of the body where unstriped muscle had been previously known to occur, and also in situations, such as the iris and the skin, where its existence had before been only matter of conjecture, but where the characteristic form of the fibre-cells, and of their 'rod-shaped' nuclei had enabled him to recognize it with precision. Confirmations of this view of the structure of involuntary muscular fibre were afterwards received from various quarters, one of the most important being the observation made in 1849 by Reichert, a German histologist, that dilute nitric or muriatic acid loosens the cohesion of the fibre-cells, and enables them to be isolated with much greater facility. In 1852 I wrote a paper 'On the Contractile Tissue of the Iris', published in the *Microscopical Journal*, in which I gave an account of the involuntary muscular fibre contained in that organ in man and some of the lower animals, stating that the appearances I had met with corresponded exactly with Kölliker's descriptions, and illustrating my remarks with careful sketches of several fibre-cells from the human iris, isolated by tearing a portion of the sphincter pupillae with needles in a drop of water. In 1853, another paper by myself appeared in the same journal, 'On the Contractile Muscular Tissue of the Skin,' confirming Kölliker's recent discovery of the '*arrectores pili*', and describing the distribution of those little bundles of unstriped muscle in the scalp. These and other investigations into the involuntary muscular tissue convinced me of the correctness of Kölliker's observations, and led me to regard his discovery as one of the most beautiful ever made in anatomy; and this is now, I believe, the general opinion of histologists.

Still, however, there are those who are not yet satisfied upon this subject. In Müller's *Archives* for 1854, is a paper by Dr. J. F. Mazonn of Kiew, in which the author expresses his belief that the muscular fibre-cells of Kölliker are created by the tearing of the tissue in preparing it, and denies the existence of nuclei in unstriped muscle altogether; but he gives so very obscure an account of his own ideas respecting the tissue, that his objections seem to me to carry very little weight, more especially as the appearances which he describes require, according to his own account, several days' maceration of the muscle in acid for their development. In June of the present year (1856), Professor Ellis of University College, London, communicated to the Royal Society of London a paper entitled 'Researches into the Nature of Involuntary Muscular Fibre'. In the abstract given in the *Proceedings* of the Society, recently issued, we are informed that, 'having been unable to confirm the statements of Professor Kölliker respecting the cell-structure of the involuntary muscular fibre, the author was induced to undertake a series of researches into the nature of that tissue, by which he has been led to entertain views as to its structure in vertebrate animals, but more especially in man, which are at variance with those now generally received.' In the 'summary of the conclusions which the author has arrived at', we find the following: 'In both kinds of muscles, voluntary and involuntary, the fibres are long, slender, rounded cords of uniform width. . . . In neither voluntary nor involuntary muscle is the fibre of the nature of a cell, but in both is composed of minute threads or fibrils. Its surface-appearance, in both kinds of muscle, allows of the supposition that in both it is constructed in a similar way, viz. of small particles or "sarcous elements", and that a difference in the arrangement of these elements gives a *dotted* appearance to the involuntary, and a tranverse striation to the voluntary fibres. . . . On the addition of acetic acid, fusiform or rod-shaped corpuscles make their appearance in all muscular tissue; these bodies, which appear to belong to the sheath of the fibre, approach nearest in their characters to the corpuscles belonging to the yellow or elastic fibres which pervade various other tissues; and from the apparent identity in nature of these corpuscles in the different textures in which they are found, and especially in voluntary, as compared with involuntary muscle, it is scarcely conceivable that in the latter case exclusively they should be the nuclei of oblong cells constituting the proper muscular tissue.'

Mr. Ellis, then, agrees with Mazonn in believing that the tapering fibre-cells of Kölliker owe their shape to tearing of the tissue; and he regards the nuclei as mere accidental accompaniments of the proper muscular structure, probably belonging to the sheath of the fibres, which, according to him, are of rounded form and uniform width.

The distinguished position of Mr. Ellis as an anatomist makes it very desirable that his opinion on this important subject should be either confirmed or refuted, and the object of the present paper is to communicate some facts which have recently come under my observation, and which, I hope, may prove to others as unequivocally as they have done to myself, the truth of Kölliker's view of this question.

In September last, being engaged in an inquiry into the process of inflammation in the web of the frog's foot, I was desirous of ascertaining more precisely the structure of the minute vessels, with a view to settling a disputed point regarding their contractility.

Having divided the integument along the dorsal aspect of two contiguous toes, I found that the included flap could be readily raised, so as to separate the layers of skin of which the web consists, the principal vessels remaining attached to the plantar layer. Having raised with a needle as many of the vascular branches as possible, I found, on applying the microscope, that they included arteries of extreme minuteness, some of them, indeed, of smaller calibre than average capillaries. A high magnifying power showed that these smallest arteries consisted of an external layer of longitudinally arranged cellular fibres in variable quantity, an internal exceedingly delicate membrane, and an intermediate circular coat, which generally constituted the chief mass of the vessel, but which proved to consist of neither more nor less than a single layer of muscular fibre-cells, each wrapped in a spiral manner round the internal membrane, and of sufficient length to encircle it from about one and a half to two and a half times. Fig. 18 (Plate II) represents one of these vessels as seen under a rather low power, and shows the general spiral arrangement of the fibres of the middle coat. Fig. 19 is a camera-lucida sketch of the same artery highly magnified, in which I have for the most part traced the outline of the fibres on the nearer side of the vessel only, but one fibre-cell is shown in its entire length wrapped round nearly two and a half times in a loose spiral. In some other vessels the muscular elements were arranged in closer spirals, as in Figs. 20 and 21. They are seen to have more or less pointed extremities, and are provided with an oval nucleus at their broadest part, discernible distinctly, though somewhat dimly, without the application of acetic acid. The tubular form of the vessels enables the observer, by proper adjustment of the focus, to see the fibre-cells in section ; they are then observed to be substantial bodies, often as thick as they are broad, though the latter dimension generally exceeds the former. Here and there a nucleus is so placed in the artery as to appear in section with the fibre-cell, as shown in Figs. 20, 22, and 23. The section of the nucleus is in such cases invariably found surrounded by that of the substance of the fibre-cells, though occasionally placed eccentrically in it. From the circular form of its section the nucleus appears to be cylindrical. These fibre-cells are from 1–200th of an inch to 1–100th of an inch in length, from 1–2500th of an inch to 1–2000th of an inch in breadth, and about 1–2500th of an inch in thickness, measurements on the whole rather greater than those given by Kölliker for the human intestine, the chief difference being that in the frog's arteries they are somewhat broader and thicker.

Now, the middle coat of the small arteries is universally admitted to be composed chiefly of involuntary muscular fibre ; but in the vessels just described it consists of nothing whatever else than elongated, tapering bodies, corresponding in dimensions with Kölliker's fibre-cells, and each provided with a single cylindrical nucleus embedded in its substance. Considering, then, that no tearing of the tissue had been practised in the preparation of the objects, but that the parts were seen undisturbed in their natural relations, it appeared to me that the simple observation above related settled the point at issue conclusively.

It was, however, suggested to me by an eminent physiologist, that the various forms in which contractile tissue occurs in the animal kingdom forbid our drawing any positive inference regarding the structure of human involuntary muscle from an observation made on the arteries of the frog. Being anxious to avoid all cavil, and understanding that Mr. Ellis's researches had been directed chiefly to the hollow viscera, I thought it best to examine the tissue in some such organ. For this purpose I obtained a portion of the small intestine of a freshly killed pig, selecting that animal on account of the close general resemblance between its tissues and those of man. The piece of gut happened to be tightly contracted, and on slitting it up longitudinally, the mucous membrane, which was thrown into loose folds, was very readily detached from the subjacent parts. I raised one of the thick, but pale and soft fasciculi of the circular coat, and teased it out with needles in a drop of water, reducing it without difficulty to extremely delicate fibrils. On examining the object with the microscope, I found that it was composed of involuntary muscular fibre, almost entirely unmixed with other tissue, reminding me precisely of what I had seen in the human sphincter pupillae, except that the appearances were more distinct, especially as regards the nuclei, which were clearly apparent without the application of acetic acid. Several of the fibre-cells were isolated in the first specimen I examined, each one presenting tapering extremities about equidistant from a single elongated nucleus. The fibre-cells were of soft and delicate aspect, generally homogeneous or faintly granular, with sometimes a slight appearance of longitudinal striae, such as is represented in Fig. 4.

I had now seen enough to satisfy my own mind that the involuntary muscular fibre of the pig's intestine was similarly constituted with that of the human iris and the frog's artery: but before throwing up the investigation, I thought it right to examine carefully some short, substantial-looking bodies of high refractive power, which at first sight appeared, both from their form and the aspect of their constituent material, totally different in nature from the rest of the tissue. Several of these bodies are represented in Figs. 10–15. Each is seen to be of somewhat oval shape, with more or less pointed extremities, and presents several strongly marked, thick, transverse ridges upon its surface; and each, without exception, possesses a roundish nucleus whose longer diameter lies across that of the containing mass. Yet between these bodies and the long and delicate homogeneous fibre-cells above described, every possible gradation could be traced. Figs. 8 and 9 are somewhat longer than those just indicated, and are also remarkable for their regularity. In Figs. 5, 6, and 7 are represented fibre-cells of considerable length, marked here and there with highly refracting transverse bands, in the intervals of which they are of soft and delicate aspect. In several cells one half was short, with closely approximated rugae, the other half long and homogeneous. Hence it was pretty clear that the appearances in question were due to contraction of the fibre-cells, and that the shortest of these bodies were examples of an extreme degree of that condition; their substantial aspect and considerable breadth being produced by the whole material of the long muscular elements being drawn together into so small a compass. The rounded appearance of the nuclei was accounted for by supposing either that they had themselves contracted, or that they had been pinched up by the contracting fibres, of which explanations the latter appears the more probable.

In order to place the matter if possible beyond doubt, I prepared two contiguous portions of the circular coat of a contracted piece of intestine in different ways; the one by simply cutting off a minute portion with sharp scissors, so as to avoid as much as possible any stretching of the tissue, the other by purposely drawing out a fasciculus to a very considerable length, and then teasing it with needles. In the former preparation, the fibre-cells appeared all of them more or less contracted, except in parts where the slight traction inseparable from any mode of preparation had stretched the pliant tissue, which in the fresh state appears to yield as readily to any extending force as does a relaxed muscle of a living limb. In the other object, where the tissue had been purposely stretched, most of the fibre-cells were extended, and possessed elongated nuclei. Here and there one would be seen of excessive tenuity, scarcely broader at its thickest part than the nucleus, looking, under the highest magnifying power, like a delicate thread of spun glass. To how great a length the fibre-cells admit of being drawn out in this way without breaking I cannot tell. Fig. 1 represents a portion of such a fibre with the contained nucleus. Among these extended fibres, however, there lay, here and there, an extremely contracted one, the result, I have no doubt, of the irritation produced by the needles upon the yet living tissue. In order to guard against this source of fallacy, I kept a piece of contracted gut forty-eight hours, and then examined two contiguous parts of the circular coat in the way above described. The muscle was much less readily extended than in the fresh state, and I found that, where stretching of the tissue had been avoided as much as possible, it was composed entirely of fibre-cells marked with transverse ridges of varying thickness and proximity; a minute fibril having, under a rather low power, the general aspect represented in Fig. 17. But I saw no distinct examples of the extreme degree of contraction so frequent in muscle from the same piece of intestine in the fresh state. This confirmed my suspicion that the latter had been induced by the irritation of the mode of preparation. On the other hand, a fully stretched fasciculus showed its fibres everywhere destitute of transverse rugae, so that the point was now distinctly proved. Kölliker, in his original article in the *Zeitschrift für wissenschaftliche Zoologie*, figured some long fibre-cells with transverse lines upon them,—' knotty swellings ', as he termed them, which he supposed probably due to contraction, and he repeats this hypothesis in the part of his *Mikroskopische Anatomie* published in 1852. The *proof* of the correctness of this idea is now, I believe, given for the first time.

The bearings of these observations on the main question respecting the structure of involuntary muscular fibre are obvious and important. In the first place, if the short, substantial bodies were mere contracted fragments of rounded fibres of uniform width, we should expect them to be as thick at their extremities as at the centre, instead of which they are always more or less tapering, and often present a very regular appearance of two cones applied to each other by their bases. Secondly, the uniform central position of the nuclei in the contracted fibres, proves clearly that the former are no accidental appendages of the latter, to which it seems difficult to refuse Kölliker's appellation of *cells*.

The effect of acetic acid on the involuntary muscular tissue is to render the fibres indistinct, but the nuclei more apparent ; and if this reagent be applied to a piece of contracted muscle, many of the nuclei are seen to be of more or less rounded form. The deviation of the nuclei from the ' rod-shape ' has hitherto been a puzzling appearance, but is now satisfactorily accounted for.

In examining a fasciculus that had been fully stretched, forty-eight hours after death, I met with several good specimens of isolated fibre-cells, two of which are represented in Figs. 2 and 3. I would draw particular attention to the delicate, spirally twisted extremities of the fibre-cell 3, such as no tearing of a continuous fibre could possibly have produced. Though these fibres are very long, yet we have no reason to believe that anything near the extreme degree of extension has been attained in them, and we cannot but contemplate with amazement the extent of contractility possessed by this tissue.

In Fig. 16 is represented a portion of a fibre-cell curled up, which has been introduced for the sake of the clear manner in which it shows the position of the nucleus embedded in it. Just as in the case of the fibres wrapped round the arteries of the frog's foot, this cell might be seen in section by proper adjustment, and that section is observed to be oval ; proving that the fibre is not round, but somewhat flattened. It happens that the nucleus appears at this point ; its section is circular, and is surrounded on all sides by the substance of the cell.

The pig's intestine seems to be a peculiarly favourable situation for the investigation of unstriped muscle. Judging from Kölliker's measurements, the fibres appear to be of much larger size there than in the same situation in the human body. The length of the fibre-cell 3 is 1-37th of an inch. The fibre 2 is imperfect at one extremity ; but, taking the double of the distance from its pointed end to the nucleus, its length is 1–33rd of an inch. These measurements are between three and four times greater than any which Professor Kölliker has given for the human intestine, and considerably exceed the length of the 'colossal fibre-cells' which he describes as occurring in the gravid uterus. The individual fibre-cells, with their nuclei and transverse markings, if they have any, are quite distinctly to be seen with one of Smith and Beck's $\frac{4}{10}$ object-glasses. But in order to examine their structure minutely, a higher power is required: that which I use is a first-rate $\frac{1}{12}$, made several years ago by Mr. Powell of London. All the figures in Plate II, except 17 and 18, are from camera-lucida sketches, reduced to the same scale. The principal measurements of the fibre-cells from the pig's intestine are as under :—

Length of fibre-cell, 3	$\frac{1}{37}$ inch.
Breadth of ditto	$\frac{1}{3300}$,,
Length of nucleus of ditto	$\frac{1}{1000}$,,
Breadth of ditto	$\frac{1}{8000}$,,
Breadth of fibre-cell, 16	$\frac{1}{3000}$,,
Thickness of ditto	$\frac{1}{4000}$,,
Length of fibre-cell, 13	$\frac{1}{750}$,,
Breadth of ditto	$\frac{1}{1250}$,,
Longitudinal measurement of nucleus of ditto . .	$\frac{1}{5500}$,,
Transverse, ditto	$\frac{1}{3500}$,,
Length of fibre-cell, 15	$\frac{1}{1000}$,,

Hence it appears that the length of the most contracted fibre-cell is the same as that of the nucleus of an extended one. The fibres vary somewhat in breadth, independently of the results of contraction. Thus, one in the extended condition which I sketched, but which is not here shown, measured only 1–4000th of an inch across. The nuclei of the uncontracted fibres are very con-constantly of the same length, and are good examples of the rod-shape to which Kölliker has directed particular attention. They always possess one or two nucleoli, and have often a slightly granular character; occasionally, as in Fig. 21, they present an appearance of transverse markings. One frequently sees near the nucleus of a fibre that has been artificially extended from the contracted state, an appearance of a gap in the substance of the cell, forming a sort of extension of the nucleus, as if the fibre generally had been stretched more completely than the nucleus: an example of this is presented by Fig. 7. Mr. Ellis lays great stress on a dotted appearance which he considers characteristic of involuntary muscular fibre. I must say I agree with Kölliker in finding the fibre-cells, for the most part, homogeneous when extended, or faintly marked with longitudinal striae.[1] No doubt dots are present in abundance; but these, so far as I have observed them in the pig's intestine, are distinctly exterior to the fibres, though adherent to their surface; and I suspect them to be little globules of a tenacious connecting fluid. That the fibre-cells do stick very tightly together may be seen by drying a minute portion of the tissue, after which they will be found shrunk, and slightly separated from one another, but connected more or less by minute threads.

To sum up the general results to which we are led by the facts above mentioned. It appears that in the arteries of the frog, and in the intestine of the pig, the involuntary muscular tissue is composed of slightly flattened elongated elements, with tapering extremities, each provided at its central and thickest part with a single cylindrical nucleus embedded in its substance.

Professor Kölliker's account of the tissue being thus completely confirmed in these two instances, and the description here given of its appearance in the arteries of the frog's foot being an independent confirmation of the general doctrine, there seems no reason any longer to doubt its truth.

It further appears, that in the pig's intestine the muscular elements are, on the one hand, capable of an extraordinary degree of extension, and, on the other hand, are endowed with a marvellous faculty of contraction, by which they may be reduced from the condition of very long fibres to that of almost globular masses. In the extended state they have a soft, delicate, and usually homogeneous aspect, which becomes altered during contraction by the supervention of highly refracting transverse ribs, which grow thicker and more approximated as the process advances. Meanwhile, the 'rod-shaped' nucleus appears to be pinched up by the contracting fibre till it assumes a slightly oval form, with the longer diameter transversely placed.

I will only further remark that these properties of the constituent elements of involuntary muscular fibre explain, in a very beautiful manner the extraordinary range of contractility which characterizes the hollow viscera.

[1] The longitudinal striae above referred to are probably due to a fine fibrous structure in the substance of the fibre-cells. When in London, last Christmas, I had, through the kindness of Dr. Sharpey, the opportunity of examining a specimen of muscle from the stomach of a rabbit, which he had prepared after Reichert's method. The nitric acid had not only detached the fibre-cells from one another, but also brought out very distinctly in each muscular element the appearance of minute parallel longitudinal fibres, which seemed to make up the entire mass of the fibre-cell except the nucleus. In a plate accompanying the paper on the Iris, before referred to, I gave figures of some fibre-cells with distinct granules arranged in longitudinal and transverse rows. This appearance, which, however, so far as my experience goes, is exceptional, and is hardly sufficiently marked to deserve the appellation 'dotted', is probably caused by unequal contractions in the constituent material.—April 2, 1857.

EXPLANATION OF PLATE II

Fig. 1 represents part of a fibre-cell from the pig's intestine, drawn out into a very fine thread.

Figs. 2 and 3, fibre-cells from the same situation, considerably extended.

Fig. 4, fibre-cells exhibiting faint longitudinal striation.

Figs. 5, 6, and 7, fibre-cells imperfectly contracted.

Figs. 8 and 9, small fibre-cells considerably contracted.

Figs. 10, 11, 12, 13, 14 and 15, fibre-cells extremely contracted.

Fig. 16, a fibre-cell curled up, showing the position of the nucleus embedded in its substance.

Fig. 17, part of a moderately contracted fasciculus of unstriped muscle from the pig's intestine, as seen under a rather low magnifying power.

Fig. 18, a small artery from the frog's web, under a rather low magnifying power.

Fig. 19, part of the same vessel highly magnified, showing the spiral arrangement of the muscular fibre-cells.

Figs. 20 and 21, muscular fibre-cells from another artery. In Fig. 20, the spirals are much closer than in Fig. 19; and in Fig. 21, the spiral is quite close.

Figs. 22 and 23 represent some fibre-cells in arteries of extreme minuteness, and show the section of the nucleus surrounded by that of the fibre-cell.

(The Figures all magnified 50)

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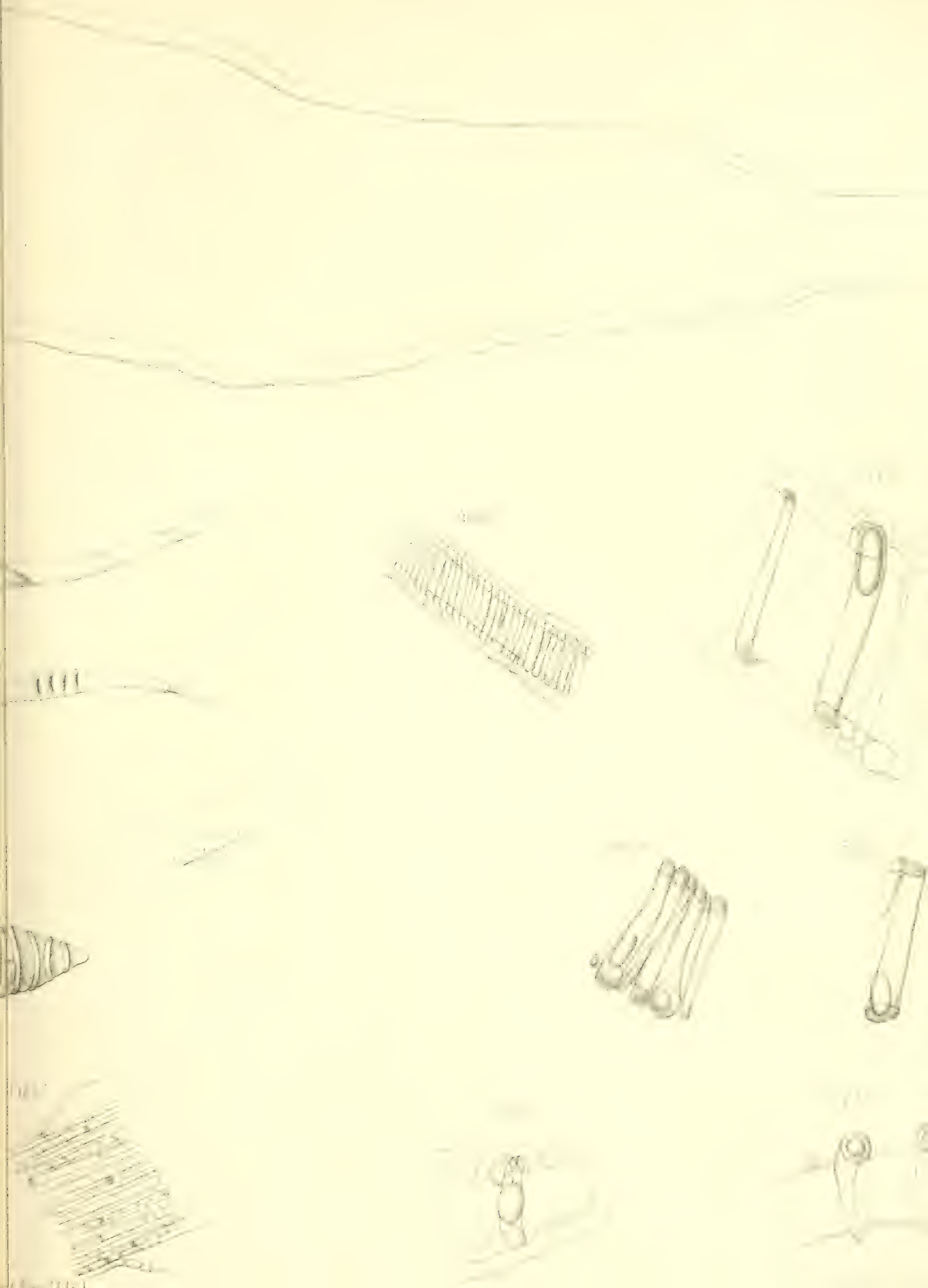


ON THE FLOW OF THE LACTEAL FLUID IN THE MESENTERY OF THE MOUSE

[*Report of the Meeting of the British Association, Dublin*, 1857, p. 114.]

THE objects of the experiments were twofold—first, to ascertain the character of the flow of the chyle under ordinary circumstances, which he believed had never yet been satisfactorily done ; and, secondly, to endeavour to throw some light upon the debated question, whether or not the lacteals were capable of absorbing solid matter in the form of granules visible to the human eye. In the first set of experiments,[1] a mouse having been put under the influence of chloroform an hour or two after partaking of a full meal of bread and milk, the abdomen was laid open by a longitudinal median incision, and a fold of intestine drawn out gently so that it might lie on a plate of glass under the microscope, the exposed part being occasionally moistened with water of the temperature of 100° Fahr. Under these circumstances, the lacteals were very readily visible as beautiful transparent beaded cords ; the beads corresponding to the situations of the valves, which were seen to be standing open, while chyle-corpuscles moved on through the tubes with perfectly equable flow, as a rule equal to about a quarter of that at which the blood moves through the capillaries. These observations were frequently repeated, and always with the same result. Hence it was clear that the lacteals, though known to be muscular, and richly provided with valves, do not, in the mesentery at least, promote the flow of the chyle by contraction, rhythmical or otherwise ; and that the source of the movement of the fluid is some cause in constant and steady operation. It was further observed that the chyle-corpuscles were, many of them, already of full size, although at so short a distance from the scene of absorption, proving the rapidity with which those corpuscles are elaborated.

The other set of experiments were performed in the same way, except that some coloured material, generally indigo, was mixed with the bread and milk. The animals took the mixture readily, and it passed freely along the intestines, but no indigo particles were ever seen in the chyle, although, had it been absorbed

[1] The experiments were made in 1853.

in the solid form, it would have been detected with the utmost facility within the lacteals. It might be supposed that the colouring matter had acted as a poison, and paralysed the function of absorption ; but there was no appearance of this, the chyle flowing just as rapidly as when the mice were fed with simple bread and milk. The facts, though not perhaps absolutely conclusive, seemed to throw great doubt on the possibility of absorption of solid matter by the lacteals.

AN INQUIRY REGARDING THE PARTS OF THE NERVOUS SYSTEM WHICH REGULATE THE CONTRACTIONS OF THE ARTERIES

[*Philosophical Transactions*, Part II for 1858, p. 607.]

Received June 18—Read June 18, 1857.[1]

GREAT light has been thrown in recent times upon the nature of the influence exercised over the blood-vessels by the nervous system. In 1852 it was shown by M. Bernard that division of the sympathetic nerve in the neck of a cat, or other mammalian, was followed by turgescence of the blood-vessels of the ear, and increased heat of that part and of the whole side of the face, together with contraction of the pupil. Early in the following year Mr. Augustus Waller performed the converse experiment of galvanizing the sympathetic above the point where it had been cut or tied, with the very striking result of rapid subsidence of the turgescence of the vessels, and fall of the temperature of the face; while the pupil became so extremely large, as to imply that the dilating fibres of the iris were thrown into a state of energetic contraction.[2]

From these experiments it appeared to follow pretty clearly that the sympathetic nerve in the neck presides over the contraction of the vessels of the face, which, becoming relaxed and dilated when the influence of the nerve was removed by its division, allowed the blood to flow through them in larger mass than before; but on the other hand, when excited to extreme constriction by the galvanic stimulus applied to the nerve, permitted but little blood to pass. This conclusion appears to be confirmed by the observation since made by Brown-Séquard, that the elevation of temperature which occurs in Bernard's experiment is never greater than is to be accounted for by the increased mass of warm blood which must be sent through the part, on the hypothesis that the turgescence of the vessels is simply the result of their dilatation. It was further shown by Messrs. Waller and Budge, that the same region of the spinal cord which they had previously ascertained to preside over dilatation of the pupil,

[1] This paper, and that on the 'Cutaneous Pigmentary System of the Frog' (p. 48 of this volume), were read as supplements to the 'Essay on the Early Stages of Inflammation' (p. 209 of this volume). The author has since extended his investigations into the subject of the present memoir, in accordance with a recommendation from the Council, and the results have been incorporated into the text, all new matter thus introduced being indicated as such either by date or by note at the foot of the page.

[2] *Comptes Rendus*, vol. xxxvi, p. 378.

namely, the part included between the last cervical and third dorsal vertebrae, also regulated the vessels of the face. When that part of the cord was removed, turgescence of those vessels occurred ; but galvanizing the anterior roots of the spinal nerves proceeding from that part produced the same effect as irritation of the sympathetic, namely, pallor with diminished temperature.[1] M. Schiff afterwards ascertained, that after destruction of the lower part of the cervical and upper part of the dorsal region of the cord in bats, there is an immediate dilatation of the small vessels of the wings,[2] and Brown-Séquard had previously shown that after transverse section of the spinal cord in the lumbar region in birds and mammals, an increase of 1°, 2°, or 3° Fahr. took place in the temperature of the paralysed parts.[3] All these facts tend to the same conclusion, namely, that the spinal cord is the part of the nervous centres which presides over the blood-vessels, and that one important action at least which it induces in them is constriction of the circular coat of the arteries. But there still remains, I believe, some difference of opinion with regard to the interpretation of Bernard's experiment ; and there might be some colour for the idea that the red and turgid state of the vessels seen after division of the sympathetic in the neck was due to a change in the blood, such as occurs in inflammation, and that the pallor ensuing upon galvanizing the nerve was the result of a return of the vital fluid to its normal condition after restoration of nervous influence. But all ambiguity of this kind seems to me to be removed by some observations made several years ago by Mr. Wharton Jones upon the frog. This animal is peculiarly adapted for investigations on this subject, because both the calibre of the vessels and the state of the blood as it flows through them can be observed with the utmost facility in the web ; and Mr. Jones found that division of the sciatic nerve was followed by dilatation of the arteries, but that this increase of calibre, so far from being caused by an obstruction in the progress of the blood, was accompanied with unusually free and rapid flow through the capillaries.[4] But with regard to the part of the nervous system which regulates the contractions of the arteries, some more recent observations by the same author are at variance with the conclusion above drawn from experiments by others upon mammalia. For he states that the division of the roots of the sciatic nerve within the spinal canal failed to produce dilatation of the vessels ; whence it was inferred that the sympathetic fibres of the sciatic trunk, as distinguished from those derived from the cord, are the channels through which

[1] *Comptes Rendus*, vol. xxxi, pp. 377, 575.

[2] *Gazette Hebdomadaire de Méd. et de Chir.*, 1854, pp. 421, 424.

[3] *Experimental Researches*, New York, 1853, p. 8.

[4] 'Essay on the State of the Blood and the Blood-vessels in Inflammation,' by T. Wharton Jones, Esq., F.R.S. *Guy's Hospital Reports*, vol. viii, p. 12.

the stimulus is transmitted to the arterial coats.[1] Waller and Budge's experiments, on the other hand, appear to show that it is from the cord that the sympathetic derives its controlling power over the arteries. This discrepancy upon a matter of such great importance in physiology appeared to me to demand further inquiry,[2] and I propose in the present paper to communicate the result to which this investigation has led.

The first experiment which I performed with reference to this subject (October 27, 1856), namely, division of the sciatic nerve on one side, gave somewhat puzzling results. Knowing how difficult it is to judge correctly of differences of calibre in the vessels by mere inspection, I tied out both feet of a frog (under chloroform), so that a slight movement of the stage of the microscope would bring either into view, and thus, after performance of the operation in one limb, the other foot might serve as a standard of comparison. I then selected a particular artery of the left foot for measurement with the eyepiece micrometer, and, having noted the limits between which its calibre varied during half an hour, isolated the nerve from surrounding parts by dissection, without any material change taking place in the diameter of the vessel. I next tied a piece of thread tightly round the nerve, with the effect of causing within the first few seconds distinct constriction of the artery, which then gradually expanded, and within two minutes had a larger measurement than I had previously observed. In other words, the effect of the ligature had been constriction speedily followed by dilatation. But on examining the web half an hour later, I found the artery had contracted again to about its usual proportions; after a few minutes the amount of constriction was very considerably greater, and continued so after division of the nerve above the ligature, and on looking at the other foot I found the arteries there similarly contracted. During the next twenty-four hours I made frequent careful comparisons of the conditions of the arteries in the two feet, and found that they presented exactly the same variations in calibre; being sometimes closely constricted, at other times fully dilated in both. The constrictions generally commenced a very short time before a struggle of the animal, and gradually subsided when it had become quiet. It was thus evident that the arteries had experienced no

[1] 'Observations on the State of the Blood and the Blood-vessels in Inflammation,' *Med. and Chir. Trans.*, vol. xxxvi.

[2] Since this paper was read, my attention has been called by Professor Goodsir to experiments recently performed by Pflüger. Operating upon the large edible frog of the continent (*Rana esculenta*), he succeeded in applying the galvanic stimulus to the anterior roots of the sciatic nerve within the spinal canal, with the effect of causing complete constriction of the arteries of the webs. Division of the same roots, on the other hand, was followed by full dilatation of the vessels (see Henle and Meissner's *Bericht*, 1857). Clear proof had thus been given, before my investigation of the subject commenced, that the spinal system does influence the arteries of the frog's foot.

permanent dilatation whatever from the division of the sciatic nerve, a result quite at variance with the experience of previous observers.

The explanation of this will shortly appear. On April 8, 1857, I laid open the spinal canal of a frog in its entire length, and divided, as I supposed, all the roots of the nerves coming off from the left side of the cord from the occiput to the sacrum, and immediately examined the webs of both feet, the frog being under the influence of chloroform. In the right limb the circulation was almost entirely arrested, while in the left it was going on freely. My attention was then diverted for half an hour, when the arteries of the right foot were found of medium size ; but in all the three webs of the left foot they were extremely dilated, appearing to have two or three times the diameter of those of the right limb.[1] This observation was of itself sufficient to prove that the spinal system, as distinguished from the sympathetic, does influence the contractions of the arteries of the frog's foot. Here, however, as in the case of the divided sciatic nerve, the effects were not permanent. Six hours later the arteries on the left side appeared smaller than they had been, though still bearing marks of the operation by remaining constant in calibre, whereas those of the right foot exhibited very frequent variations, from pretty full dilatation to almost absolute closure. Next day the same state of things continued, the vessels of the left foot being constant in size for four minutes together, while in the right foot an artery exhibited about eight distinct variations of calibre per minute as observed by micrometer ; but after three days more they had become both small and variable in the left foot, and seemed to have quite recovered. On the application of galvanism to the cord, however, both legs were thrown into violent spasm, showing that communications still existed between the left limb and the nervous centre ; and it appeared probable that the branches which remained undivided had come after a while to supply more or less perfectly the place of those which had been cut. A similar explanation seemed applicable to the speedy recovery of contractility in the vessels after cutting the sciatic, other nerves in the limb supplying the place of the divided trunk.

In another experiment, performed on the 11th of April, the roots of the nerves on the right side were divided within the spinal canal, beginning at the head and proceeding gradually backwards. No enlargement of the vessels of the webs occurred until the roots of the sciatic plexus were cut, when full

[1] In this and other cases of division of roots of the spinal nerves, I observed that the skin of the limbs supplied by the nerves cut became perfectly smooth, instead of being, as usual, rough with minute papillae. This appears to show that the unstriped muscular tissue of the skin is under control of the spinal system.

dilatation of the arteries of the right foot took place, one which had a few minutes previously varied from 1 to 2 degrees of the eyepiece micrometer being now $3\frac{1}{2}°$ in diameter, and remaining so for ten minutes together. Half an hour later, however, I was astonished to find the artery again contracted to $2°$, and not quite constant in calibre. But next day, on dissecting the animal, I found that some branches of considerable size between the cord and the sciatic plexus remained entire.

This experiment, while confirming the proof of the influence exerted by the cord over the arteries of the feet, convinced me how difficult it is to make sure of dividing all the roots of the nerves for the hind legs within the spinal canal; the operation being a very delicate one, while the parts are obscured by the bleeding which occurs in the living animal. At the same time the speedy recovery of function after partial division of the roots, pointed out a ready source of fallacy in such experiments. Had I deferred the examination of the web for half an hour in this case, there would have been no evidence of any effect produced on the vessels by the operation, and yet, had it not been for dissecting the frog, I should not have doubted that all the roots had been severed.

Dilatation of the vessels of the webs having been found to follow division of the roots of the spinal nerves, it appeared important, in order to complete the evidence on the point at issue, to observe the occurrence of contraction in the arteries on irritation of the cerebro-spinal centre. For this purpose, on the 14th I laid open the cranium of a frog under chloroform and thrust a very fine needle into the cerebral hemispheres, while one of the feet was stretched under the microscope: no effect was, however, produced upon the arteries; one selected for micrometrical observation, the largest of the web, measuring, as it had done before, nearly $4°$, which was a state of full dilatation. I then treated in a similar manner the posterior dark-coloured portion of the brain, including the optic lobes, cerebellum, and medulla oblongata, which were not distinguished from one another in the experiment. As I continued this treatment for a few seconds, keeping my eye over the microscope, the artery became contracted to $1°$, which was the length of a red corpuscle. The leg then became spasmodically extended, and the artery was carried out of the field; but when I next looked at the web after removal of the needle, the vessels had dilated again to pretty full size. Having selected a main artery of another web more conveniently placed, I repeated the experiment of thrusting the needle into the posterior portion of the brain. This vessel, which just before, though by no means at its largest size, measured $2\frac{1}{2}°$, became contracted to almost absolute closure, and remained so till the needle was removed, after which it gradually dilated, and in three minutes measured $2°$; forty seconds later $2\frac{1}{2}°$;

and about a minute afterwards 3°. The experiment was repeated several times with similar results, 'the invariable rule' (to quote from my notes) 'being contraction of the artery up to a certain point, and maintenance in the contracted state during the *whole* time, often several minutes, that the needle was stirred about in the brain; and then expansion, beginning almost immediately after withdrawal of the needle, and advancing to a certain point at which it remained till the needle was again introduced.' As the brain became more and more broken up, the contractions grew less and less energetic, and the dilatations were increased, till the needle failed to produce greater contraction than from 4° to 3°. I then thrust the needle into the spinal canal and withdrew it immediately. The hind legs started, and, after a few seconds, when I first caught sight of one of the webs, it was almost bloodless, and the arteries were invisible through extreme constriction. Four minutes later the artery before observed had begun to dilate and measured 1°, and after five minutes more it was 3°. A repetition of this experiment produced similar effects.[1]

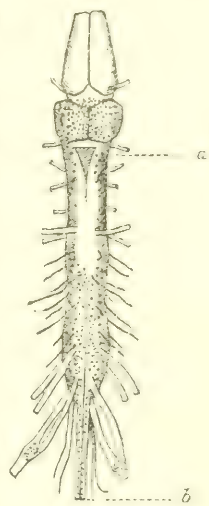
Abundantly sufficient proof had now been obtained that the cerebro-spinal axis does contain a nervous centre for regulating the contractions of the arteries of the feet. But it was uncertain whether that centre were confined to any one part of the cord, or diffused extensively through it and the brain; or even whether a similar office might not also be discharged by some of the sympathetic ganglia. With a view to determining these points, which are of great physiological interest, several experiments were performed, some of which it will be necessary to relate; but in order to make their description intelligible, it will be well to say a few words regarding the arrangement of the spinal cord in the frog. It does not occupy the entire length of the spinal canal, but extends backwards only seven-tenths of the distance from the occiput

[1] The constriction of the arteries of the webs on irritation of the cord may be readily demonstrated in the following simple manner. The head of the frog being depressed so as to stretch the ligament between the occiput and first vertebra, a sharp knife is carried across the spinal canal immediately behind the head, so as to divide the cord from the brain. The toes may now be tied out and any observation made upon the web without the inconvenience generally produced by voluntary struggles on the part of the animal, while at the same time the use of chloroform is avoided; which is very desirable, on account of the irritating effect of its vapour on the web and the constant care required for its administration. If the webs be examined immediately after the operation, they will be found exsanguine from extreme constriction of the arteries; but in a few minutes this state will give place to dilatation with free flow of blood. If now a fine needle, curved at the end, be introduced through the wound into the spinal canal, so that its point may penetrate a short distance into the cord, while the eye of the observer is kept over the microscope, the arteries will be seen to become constricted to absolute closure, and dilate again after withdrawal of the needle. The experiment may be repeated as often as may be desired till the cord becomes disorganized.

I have lately found the above-mentioned mode of preparing the frog the best adapted also for experiments elucidating the nature of inflammation. Little if any reflex action of the limb occurs when irritants are applied to the web; and if no great amount of blood have been lost in the operation, the creature will survive it a long while, e.g. eight days in one case.

to the sacrum, while the posterior three-tenths of the canal contain merely the cauda equina, including a slender filiform prolongation of the cord, which, though apparently composed in part of nervous matter, seems to give off no nerves.

In the accompanying sketch of the superior aspect of the brain and cord of a frog, magnified two diameters, the distance from *a* to *b* represents the length of the spinal canal. The principal nerves for the hind legs spring from the cord near its extremity, but other smaller branches with the same destination arise nearly as far forward as the middle of its length. There are also connecting filaments between these and some nerves for the abdominal parietes, taking origin slightly further forward than the middle of the cord. Thus the nerves for the posterior extremities are furnished chiefly, but not quite exclusively, from the posterior half of the cord. To expose the cord in its entire length without injury to it or any of its slender branches is troublesome, and also involves much loss of blood. It is therefore very desirable to be able to come at once on any part of the cord you may desire, without laying open the whole canal. This can be readily done from the data above given. The articulation between the occiput and first vertebra can be felt through the skin, as also can the commencement of the sacrum; and the distance between these points is the length of the spinal canal. This, multiplied by 0·7, is the length of the cord: the requisite fraction of this length is then measured from the occiput and gives the place required.



Assistance may also be derived from the circumstance that the posterior edges of the scapulae correspond very nearly with the mid-length of the cord, overlapping the posterior half by only about one-twentieth of the whole.

To proceed with the experiments. On the 16th of April, a large frog being put under chloroform, the entire brain was removed about 3 o'clock p.m. without injury to the cord. After this operation, the arteries, which had previously been of pretty full size and transmitting rapid streams of blood, were found completely contracted, so that the webs appeared bloodless except in the veins, and continued so for some minutes. At $3^h\ 10^m$ an artery selected for special observation was dilating, having already attained to a diameter of $1\frac{1}{2}°$, and the circulation was returning in the web. At $3^h\ 15^m$ the vessel measured 3°, but two minutes later was $2\frac{1}{2}°$, and half an hour afterwards exhibited the spontaneous changes in calibre commonly seen in arteries in health, the limits observed being $1\frac{1}{3}°$ and 2°. It thus appeared that the removal of the brain had had no further effect upon the arteries than the temporary constriction induced by the irritation of the anterior part of the cord in the operation, followed by a brief period of dilatation. At 4^h, a small part of the spinal canal having been laid open, the anterior sixth of the cord was removed, corresponding to the anterior third of the scapulae. At $4^h\ 3^m$, when the web was first looked at, the artery was contracted to absolute closure, and the web exsanguine; and this state of things continued till $4^h\ 7^m$, when the vessel began to dilate. At $4^h\ 8^m$ it measured $2\frac{1}{2}°$, and at $4^h\ 13^m$, $3°$. Four minutes later it was short of $3°$, and after five minutes more it was observed to be undergoing spontaneous variations of calibre from $2\frac{1}{2}°$ to $2\frac{2}{3}°$. Finally, at $5^h\ 30^m$ its condition was just as it was before the experiment was performed, varying from $1\frac{1}{2}°$ to $2°$, without any struggle on the part of the creature, the blood at the same time flowing rapidly through it.[1] At 6^h, another vertebral arch having been taken away, the subjacent portion of cord was removed, the canal being thus cleared as far back as the level of the mid-scapulae, corresponding to rather more than a quarter of the cord. The operation caused contraction of the artery to $1°$; but this passed off in half a minute, and was followed by no further dilatation than to $1\frac{1}{3}°$, and a few minutes later the artery was again spontaneously varying from $1°$ to $1\frac{1}{3}°$; at the same time the heart's action was somewhat enfeebled. At $6^h\ 15^m$ the portion of cord corresponding to another vertebral arch was cut away. The operation induced contraction from $1\frac{1}{3}°$ to $\frac{1}{2}°$, followed by gradual dilatation (in fifteen seconds) up to $1\frac{2}{3}°$, and this, in a few seconds, gave place to spontaneous contraction to $1\frac{1}{2}°$. By this last operation the vertebral canal had been cleared as far back as the posterior third of the scapulae, corresponding to between one-third and one-half of the length of the cord.

At $6^h\ 30^m$, having removed another vertebral arch, I divided the cord imperfectly, as far back as it was exposed, namely, at the level of the posterior edges of the scapulae, which is in the commencement of the posterior half of the cord; and on looking at the web twenty seconds later, found the artery undergoing oscillations in calibre, such as had never before been seen in it, contracting and dilating distinctly five times in a minute, from $1°$ to $1\frac{1}{3}°$ or $1\frac{1}{2}°$. At $6^h\ 32^m\ 20^s$ the cord was cut fairly through at the point indicated, without removal of the segment from the canal, and at $6^h\ 34^m$ the artery was found quite constricted and the web exsanguine. At $6^h\ 36^m\ 10^s$ the artery had somewhat dilated, and measured $1\frac{1}{3}°$, but the blood was moving very slowly through the vessels, the heart being exceedingly enfeebled. At $6^h\ 40^m$ the portion of the cord was

[1] The transient character of the effects produced upon the arterial calibre by these operations led me at first to conclude that the anterior parts of the cerebro-spinal axis did not contain any nervous centre for the arteries, and this view was expressed in the original manuscript. My opinions on this point have, however, been altered by the results of subsequent experiments, as will appear at the conclusion of the paper.

detached from the roots of the nerves which sprung from it and removed from the canal, immediately after which the artery was found dilated to $1\frac{2}{3}°$, but the blood had ceased to move in consequence of the feebleness of the heart.

The experiments upon this animal show that if the brain and anterior third of the cord act at all as nervous centres for the arteries of the feet, they are certainly not the only parts which possess that function ; and also, that irritation of any part of the anterior half of the cord gives rise to contraction of the arteries of the webs, followed by dilatation, varying much in extent and duration, but generally proportioned in both respects to the previous constriction. It is probable that the dilatation would have been greater after the last operations, had the heart been working more powerfully ; for it will hereafter appear that a certain amount of distending force on the part of the blood is necessary for the vessels becoming fully expanded.

And the 18th of April, having put a large frog under the influence of chloroform, I removed a vertebral arch opposite the junction of the middle and posterior thirds of the scapulae, and then cut across the cord in that situation, i.e. rather more than a line anterior to its middle ; a slight retraction of the two segments proved that the division had been thoroughly effected. This was at 10 o'clock a.m. A few minutes later the arteries had recovered from the effects of the irritation ; one selected for special observation, having measured $1\frac{2}{3}°$ just before the operation, now varied occasionally between $1\frac{1}{3}°$ and $1\frac{2}{3}°$, and the circulation was rapid through the vessel. The next vertebral arch posteriorly having been removed, the cord was divided as far back as it was exposed, at $10^h\ 23^m\ 50^s$; immediately after which the web was found exsanguine in consequence of complete closure of all the arteries, which continued almost in the same condition for ten minutes, at the end of which time the artery selected was still so small as to transmit single corpuscles with difficulty. At $10^h\ 35^m$ the portion of cord included between the points of section was detached from the roots of the nerves connected with it and removed from the canal. It measured nearly a line in length, and the posterior segment thus shortened proved afterwards to be only a very small fraction more than half the length of the cord. The vessels afterwards relaxed slowly, so that at $10^h\ 37^m$ the corpuscles were passing a little more freely through the artery. At $11^h\ 15^m$ the artery measured $1\frac{1}{2}°$, but transmitted the blood in a very languid stream ; and at noon the evidences of circulation were so equivocal, that I suspected the creature, which was weak to begin with, to be dead, though this afterwards proved to be a mistake. At $0^h\ 45^m$ p.m. the same state of things continued, and the artery still measured $1\frac{1}{2}°$, having remained unaltered in calibre for the last hour and a half ; but I determined to try the effect of irritating the posterior segment of the cord, and introduced the point of a needle a short distance into its anterior extremity and withdrew it immediately, keeping my eye over the microscope. The effect upon the artery was immediate constriction, causing a retrograde stream of the blood in it for about a second, and then absolute obliteration of calibre. At 0^h 49^m the artery allowed single corpuscles to pass through it with considerable difficulty. At 1 o'clock the arteries of the web were still small, but I noticed that they were undergoing very remarkable oscillations in calibre, just as occurred on one occasion in the frog last operated on, but in the present case they were more striking. I noted the variations for some time, and give in the following table a specimen of those which occurred during one minute :

	H.	M.	S.	
At	1	2	57	the diameter of the artery was $1\frac{1}{4}°$.
At	1	3	9	the diameter of the artery was $1°$.
At	1	3	20	the diameter of the artery was $\frac{1}{2}°$.
At	1	3	25	the diameter of the artery was $0°$.
At	1	3	38	the diameter of the artery was $\frac{1}{2}°$.
At	1	3	45	the diameter of the artery was $0°$.
At	1	3	50	the diameter of the artery was $\frac{1}{2}°$.

These oscillations continued for upwards of half an hour, but during the latter part of that time the extreme degrees of constriction were not observed.

At 1^h 43^m p.m. I raised the vertebral arches from the end of the spinal canal, and removed the posterior half of the cord together with the cauda equina ; immediately after which, the artery, which for the last hour had not exceeded $1\frac{1}{4}°$, became expanded to $2\frac{1}{4}°$, a dimension which it had never before been observed to attain, except during the secondary dilatation that ensued after the first division of the cord when the heart was in powerful action. All the other arteries of the web became dilated at the same time, and remained of perfectly constant diameter during the hour that I continued to observe them. Finally, at 2^h 40^m I introduced a needle into the anterior part of the spinal canal which had hitherto been undisturbed, and irritated both the anterior portion of the cord and the brain, but no effect whatever was produced upon the vessels.

The constriction of the arteries, which resulted in this case from irritation of the posterior half of the cord isolated from the rest, and the permanent dilatation which ensued on removal of the same part, prove that this portion of the cerebro-spinal axis certainly contains a nervous centre for regulating the contractions of the arteries of the feet. The frequently alternating contractions and dilatations which occurred in this animal, as well as in the last, after irritation of the posterior half of the cord, are curious, and may perhaps be considered analogous to rapid action of the heart under the influence of stimulus. The fact that the arterial contractions so constantly observed to result from irritation of the anterior part of the cord, while it retains its connexion through the rest of the cord with the roots of the nerves of the hind legs, fail to occur after removal of the posterior two-thirds of the cord, has been confirmed by subsequent experiments upon other frogs. It appears to imply that if the brain and anterior part of the cord discharge the functions of a nervous centre for the arteries of the feet, they do not exert that influence through the branches which connect them with the sympathetic, but only through the roots of the nerves given off from the more posterior parts of the cord.

On the 2nd of June, a large frog having been put under the influence of chloroform, the vertebral arches were removed, from the sacrum to the posterior edges of the scapulae, and at $0^h\ 30^m$ p.m. the cord was divided immediately behind the latter situation, i.e. a little behind its middle. The left foot being examined shortly after, the arteries were seen to be considerably constricted ; one of them, which appeared to be a principal trunk, permitting single corpuscles to pass with difficulty, and the contraction became extreme after irritation of the posterior segment of the cord with a needle. The whole of the exposed part of the cord and the cauda equina, including the chief branches of nerves for the hind legs, were then removed (at $0^h\ 56^m$), and when the foot was again looked at, at $1^h\ 10^m$, the circulation, which had been previously entirely arrested by the contraction of the vessels, was going on rapidly through dilated arteries, the one before mentioned now measuring 3°. This, however, proved not to be the extreme degree of dilatation of which the vessel was capable ; for a stream of water at about 120° Fahr., thrown for perhaps a second upon the foot, induced, after brief imperfect contraction, an expansion to nearly 4°, which again was followed after a few minutes by a return to 3°. This experiment was several times repeated. In the right foot, which had not been subjected to the hot water, though necessarily equally affected with the other by the removal of the portion of cord, the arteries were found of moderate size at $3^h\ 45^m$, having evidently recovered, to a considerable extent at least, their contractile power during the $2\frac{3}{4}$ hours which had elapsed since the operation. One which at this time measured $1\frac{2}{3}$°, became dilated on the application of hot water to 3°, and afterwards contracted spontaneously to 2°.

At $4^h\ 15^m$ an additional portion of the cord was removed, so as to clear the spinal canal as far forward as the anterior third of the scapulae. The arteries became at once dilated to some extent, notwithstanding that the heart's action was greatly enfeebled by this operation; and at $6^h\ 45^m$ they had attained nearly the full diameters that the hot water had before induced, while the circulation had somewhat recovered. Next morning the arteries of the two feet, the dimensions of which were before given, measured $4°$ and $3°$ respectively, and they continued without the slightest variation until $5^h\ 25^m$ p.m.; the circulation meanwhile had continued to improve, and was healthy, though still languid. I then removed the remainder of the cord and the entire brain without producing any effect whatever on the size of the arteries, and they still measured precisely the same at $10^h\ 45^m$ p.m. The following morning the frog was dead, and the tissues of the web had become opaque by the imbibition of water.

In this case the arteries recovered their contractile power after the removal of the greater part of the posterior half of the cord, together with the chief roots of the nerves for the hind legs; but when the part which furnishes branches to the posterior extremities had been completely removed, the arteries became permanently dilated; and, though the circulation was then feeble, soon attained the full calibre which hot water had induced at a time when the heart was in powerful action.

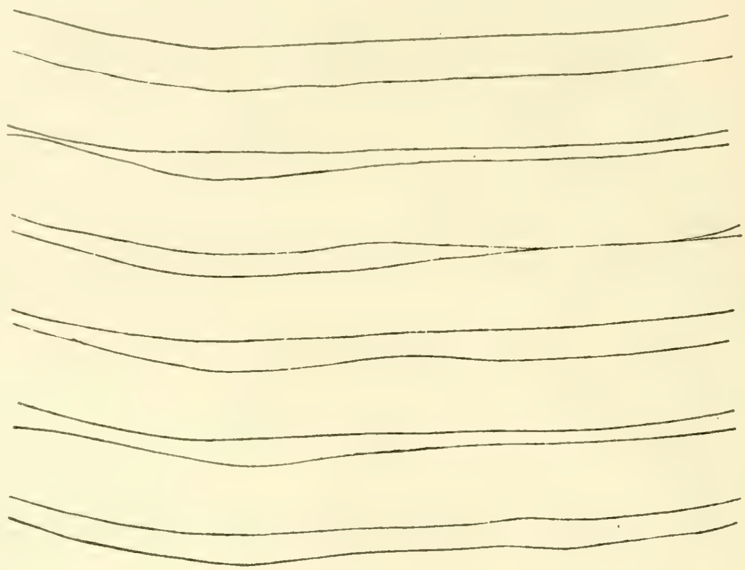
The perfect constancy with which the vessels observed maintained these dimensions for more than thirty hours after the operation, implied that they were not then at all acted on by the nervous system; and hence I was led at first to infer that there existed no other ganglionic apparatus for the arteries of the feet than that contained in the cerebro-spinal axis.[1]

I have since witnessed in other frogs the permanence of the dilatation of the arteries after removal of the brain and cord. The following case, however, appeared at first inconsistent with these observations. On the 23rd of October the brain and cord of a large frog were completely removed, and an operation was performed upon the right thigh, which, as it turned out, tended to interfere with the freedom of the circulation in the webs; so that after twelve hours, the blood, though not presenting the appearances of inflammation, was almost motionless in that foot. At the same time, two arteries in one of the webs, which had till then remained perfectly constant in calibre, as determined by micrometer, began to exhibit variations, and during the next twenty-four hours continued to change their diameter occasionally. There were, however, certain peculiarities about these changes such as I had never before seen. Generally speaking, all the arteries of a web are found in the same degree of contraction at any one time; but here, one of the vessels under observation

[1] This was the view expressed in the original manuscript, but it has been since modified by further experiments mentioned in the text, made, as their dates imply, subsequently to the reading of the paper.

was sometimes small, when the other, though in the same web, was large; and not only was there no proportion between the degrees of contraction in the two vessels, but in one and the same artery the amount of constriction was very different at different parts. The unusual character of these contractions implied that they were caused by some unwonted circumstances; and from their coincidence with the almost total arrest of the blood, as well as from the fact that in the left foot, where the circulation continued free, the arteries remained of full size till the animal was destroyed, I was led to conclude that the puzzling appearances in question must be in some way or other dependent on the cessation of the flow of the vital fluid through the vessels. If this were so, it seemed probable that the mechanism by which these irregular contractions were induced might be as local as their exciting cause, in which case they would be seen to occur in an amputated limb. In order to determine this point I made the following experiment. On April 2, 1858, having passed a knife between the brain and cord of a large frog so as to render the legs insensible, and having ascertained that the arterial constriction resulting from that operation had subsided, I placed a ligature round one of the thighs, and then amputated the limb at a higher point. The application of the ligature not only prevented the blood from escaping, but produced considerable tension in the soft parts of the thigh; and on examining the webs, I found the arteries fully dilated, one which I selected for special observation measuring $4\frac{1}{2}^{\circ}$ in diameter. At 6^{h} p.m., an hour and a half after the amputation, the vessel still maintained the same calibre, but at $7^{h}\ 35^{m}$ it was slightly less, viz. 4°, which was still its measurement at 11 o'clock. Hitherto no change distinctly referable to vital contractility had taken place, but on the following morning the vessel was reduced to 3° in diameter, and on the 4th of April it was of different sizes in different parts, viz. from $1\frac{1}{2}^{\circ}$ to 3°, and varied somewhat during the course of the day. Still more striking changes in the diameter of the artery appeared on subsequent days; thus the vessel was sometimes constricted to absolute closure in one part of its course, and dilated to a very considerable degree, e.g. $3\frac{1}{2}^{\circ}$, in another part. More commonly, however, the artery, though never uniform in size as in health, had a general tendency either to moderate constriction or dilatation. The variations occurred frequently during the twenty-four hours, and on one occasion I saw the artery in the act of slow contraction at one part driving the blood into a dilated portion at a little distance. So late as the evening of the 10th of April, i.e. during the ninth day after amputation, far later than vital contractility is generally believed to last in a limb so circumstanced, variations of calibre continued to show themselves; but on the 11th of April the vessel had an almost uniform width of nearly 3°, and exhibited no variations, while, at the same time, other evidences of loss of vitality in the tissues began to show themselves. The accompanying outlines of the calibre of a limited portion of the artery, which was the subject of special observation, have been made from micrometrical measurements selected from among a large number daily registered. They will serve to convey an idea of the more striking varieties of appearance presented at different times. It may be mentioned, that the diameter of the vessel, when most dilated, was about 4½ times the length of a red corpuscle of the frog's blood.

H. M.
April 2 ...... 6 0 p.m.
April 5 ...... 3 15 p.m.
April 7 ...... 6 7 p.m.
April 7 ...... 11 20 p.m.
April 10 ...... 5 0 p.m.
April 11 ...... 11 10 a.m.



It must be added, that the limb was kept wrapped in clean wet lint in a cool place in the intervals of the observations, and that during the periods of examination care was taken to guard against warmth or dryness, or any other agency calculated to injure the delicate tissues of the webs.

Thus irregular contractions, precisely similar to those which accompanied local arrest of the circulation in the experiment of October 23, took place in consequence of amputation of the limb; and as there could be no doubt that in both cases they were produced in the same manner, there was no longer any reason to suspect that sympathetic ganglia in the trunk might have had any share in their development in the former instance. Yet the circumstance above mentioned, that in the amputated limb the tendency to constriction usually affected a considerable tract of the vessel, and sometimes its entire length, to nearly the same degree, or in other words, that the muscular fibre-cells of the circular coat of the artery still contracted in concert with each other, seemed to imply the operation of a co-ordinating nervous apparatus contained in the limb. It appears probable that the means by which these concerted movements are induced are nerve-cells disseminated through the limb, in the same manner as Meissner has lately shown to be the case in the mammalian intestine.[1] The intestines also present a parallel to the arteries, in the fact that contractions of their unstriped muscular fibres result from arrest of the circulation in them ; and I have lately shown [2] that these movements are not due to any influence exerted directly upon the contractile tissue, but that the intestinal nerves are essential to their production. Thus we have support from analogy for the view that the muscular contractions which occur under similar circumstances in the arteries are induced by nervous agency.

The fact that the contraction produced in an artery of the frog's web by pressure upon a particular point affects a considerable extent of the vessel, instead of being limited to the spot irritated, is also an argument for the existence of a local co-ordinating apparatus ; for I find that this occurrence continues to take place in an amputated limb. The observation was made on August 4, 1858. One of the hind legs of a frog having been removed after a ligature had been passed round the thigh so as to prevent escape of the blood, pressure was made with a fine but blunt instrument over a particular point in the course of a large artery, whose calibre had previously been accurately determined by micrometer. The contractions which resulted affected the immediately adjacent parts of the vessel to an extreme degree ; the effect, however, was not limited to these, but gradually shaded off in both directions ; and even at a considerable distance, where by ordinary observation no change might have been detected, the micrometer showed a diminution from $6°$ to $5°$,[3] occurring immediately upon the irritation and subsiding soon after. Similar results were obtained on repetition of the experiment.

From the analogy of the intestinal and cardiac movements,[4] it is probable that the local co-ordinating apparatus for the arteries comes into play in all cases of arterial contraction in the living animal, and is the medium through which the nerves which arise from the cord act upon the vessels. But it is very important to bear in mind that it is, under ordinary circumstances, in entire subjection to the spinal system, and only acts independently under special conditions of local irritation.

It remained as yet undecided whether the nervous centre for the arteries contained in the cerebro-spinal axis were extensively diffused or limited to

[1] Henle and Pfeufer's *Zeitschrift*, 2nd series, vol. viii, 1857

[2] Vide 'Preliminary Account of an Inquiry into the Functions of the Visceral Nerves, &c.' (p. 90 of this volume).

[3] These degrees have a different value from those mentioned in other parts of this paper, a different micrometer having been employed.

[4] See 'Preliminary Account, &c. ', before referred to.

some particular region of it. The experiments hitherto related had revealed nothing absolutely irreconcilable with the hypothesis of a spot about the middle of the cord being the special regulator of the contractions of the vessels; a view indicated, though by no means proved, as regards the arteries of the face and fore-limbs in mammalia, by the observations of Waller and Budge and of Schiff, alluded to at the commencement of this paper. It appeared probable that this point might be readily determined by removing the middle third of the cord, and ascertaining whether or not the arteries still retained their contractility.[1] Accordingly, on August 26, 1857, having selected for measurement an artery in one of the webs of a frog, I divided the cord transversely at the distance of a quarter of its length from the posterior end, at $11^{h}\ 7^{m}$ a.m. During the next half-hour the diameter of the vessel was observed varying frequently from $\frac{1}{2}°$ to $1\frac{1}{2}°$. At $11^{h}\ 34^{m}$ the cord was again cut across opposite the middle of the scapulae, i.e. at a distance of a little more than a quarter of its length from the occiput. After this operation the artery was observed for about a quarter of an hour varying occasionally in calibre between 1° and 2°. At $11^{h}\ 53^{m}$ the portion of cord intervening between the two transverse incisions, and measuring very nearly half its entire length, was removed, immediately after which the artery measured $1\frac{1}{2}°$. At $11^{h}\ 55^{m}$ its diameter was 1°, the heart meanwhile continuing in good action, and twelve minutes later the vessel was again seen to change in calibre from 1° to $1\frac{1}{2}°$ and back again to 1°. The heart's action afterwards became very feeble, and the parts of the nervous centres concerned in regulating the arterial calibre appeared also to be failing in their functions, the vessel varying very slightly, and gradually increasing in diameter, till towards 1^{h} p.m. its measurements were from 2° to $2\frac{1}{4}°$. At $1^{h}\ 1^{m}$ the posterior end of the cord was removed, immediately after which the diameter of the artery was above $2\frac{1}{4}°$, or larger than ever seen before; at $1^{h}\ 4^{m}$ it was near $2\frac{1}{3}°$, and continued so at $1^{h}\ 10^{m}$. Soon after this the circulation ceased entirely.

In this case, notwithstanding the removal of the two middle quarters of the cord, the arteries were observed moderate in size and varying in calibre at a time when the heart was acting well. Hence it was evident that the middle portions of the cord are not essential to the regulation of the arterial contractions in the feet. The following experiment confirmed this important conclusion, and also furnished additional information.

On the 20th of October, a large frog having been placed under chloroform,

[1] In the original manuscript I was obliged to express my regret that time had not yet permitted me to carry out this idea. The dates in the text indicate that it has been done since the paper was read.

the cord was divided transversely at the distance of about one-fifth of its length from the posterior extremity. At $4^h\ 20^m$ p.m., just after the operation, an artery in the right foot measured $2\frac{1}{2}°$, the vessels appearing generally of pretty full size, and the flow of blood rapid through the web. At $4^h\ 25^m$ the cord was again cut across a little behind the mid-scapulae, at a distance from the occiput of somewhat more than a quarter of the length of the cord. At $4^h\ 33^m$ the diameter of the vessel was $1\frac{1}{3}°$. At $4^h\ 40^m$ the portion of cord included between the incisions was removed, without any interference with either the anterior or posterior segment. It was observed that a large branch for the hind legs, furnished by the middle segment, had to be divided during its removal, and immediately after the operation the artery measured $2\frac{1}{3}°$, and the flow of blood in the web was much more rapid than before. At $4^h\ 45^m$ the artery had contracted to $2°$, at $5^h\ 7^m$ it measured short of $2°$, and a minute later was again $2°$. At $5^h\ 11^m$ I introduced a fine needle into the anterior segment of the cord with the effect of causing convulsive movements of the fore legs, but no change whatever in the calibre of the artery in the hind leg. I afterwards repeated this experiment twice, and the last time carried the needle on into the brain, and stirred it up thoroughly, but no effect was produced upon the vessel. At $5^h\ 23^m$ the whole brain was removed, together with the anterior segment of the cord ; the artery, however, still continued to measure $2°$. At this time the circulation, though somewhat enfeebled, was still pretty good. At $5^h\ 53^m$ a complicated operation was performed upon the left thigh, to which I need not allude further than to mention that it no doubt involved exposure of the other foot to a higher temperature than before, in consequence of the vicinity of my hands, and this was probably the cause of the dilatation of the arteries observed immediately afterwards, that which had been previously measured being now $2\frac{2}{3}°$. Five hours later the artery was again $2°$, but the heart's action was excessively languid. Next morning the circulation was going on steadily, though somewhat slowly, the heart having obviously recovered to some extent during the night. The arteries were larger than ever seen before ; the calibre of that above noted being $3\frac{1}{4}°$, and there were a good many blood-corpuscles adhering to the walls of the vessels. It is probable that the small posterior segment of the cord had become impaired in its powers, but that it was still acting to some extent was evident from the circumstance that after its removal at $10^h\ 56^m$ a.m., the vessel was found increased to $4°$, and in consequence of the arterial dilatation, the stagnation of the red corpuscles, which existed in several parts of the webs, was almost entirely dispelled, although the action of the heart did not appear to have been changed. During the next half-hour the artery was measured four times, and was in every instance found to be still 4° in diameter. I may mention that I measured the posterior segment of the cord immediately after its removal, and found its length to be one-sixth of that of the whole cord ; it was in fact little more than the tip of it ; but allowing for a certain amount of contraction, it may be reckoned as one-fifth.

This case shows that the extremity of the cord acts as a nervous centre for the arteries. But the experiment of the 2nd of June proved that after the removal of the greater part of the posterior half of the cord, the vessels still remained under the control of the nervous system.[1] Hence it is clear that the nervous centre for the arteries is not confined to any limited region of the cord.

This experiment also indicates, in a very striking manner, how small a piece of the cord will suffice to regulate the calibre of the arteries, and how little effect may be produced, even in the first instance, by the removal of a large portion which also possesses that function. For it was shown, by the absence of contraction in the vessels when the anterior segment was irritated, and still more conclusively by the absence of dilatation when the anterior segment and the brain were removed, that the posterior segment was the only part capable of acting on the arteries after the removal of the middle segment ; or, in other words, that this operation deprived the arteries of the influence of the whole cerebro-spinal axis, except the posterior fifth of the cord. Yet, although the heart was acting powerfully at the time, the dilatation produced by this procedure was only moderate in amount, and very transient. Hence it follows that the mere fact of the speedy return of the arteries to their former state of contraction, after removal of an anterior portion of the cerebro-spinal axis, as seen in the experiment of April 16, 1857,[2] is no ground whatever for believing that such a portion does not act as a nervous centre for the arteries. This being clearly understood, the invariable occurrence of contraction, when the posterior part of the brain or the anterior half of the cord was irritated, in the experiments of April 14 and 16, 1857,[3] must be regarded as strong presumptive evidence, if not absolute proof, that they as well as the posterior half of the cord preside over the arterial contractions in the feet, although, as shown at p. 37, they appear to exert their influence only through those roots of nerves which take origin from the posterior regions of the cord. On the other hand, the cerebral hemispheres seem to take no part in this function, so far at least as it is safe to draw any inference from the negative evidence derived from a single experiment performed upon them, viz. that mentioned at p. 31.

The fact that the removal of a large portion of the cord is followed by

[1] Vide p. 37. [2] Vide p. 33. [3] Vide pp. 31, 33.

only temporary dilatation of the arteries, provided that a part remains which furnishes roots of nerves for the posterior extremities, is in harmony with the transient effects which were seen to be produced upon the vessels by partial division of the roots of the nerves within the spinal canal in the experiments of April 8 and 11, 1857.[1] In both these cases the arteries of the webs appeared to recover their contractile power completely, although the leg remained nearly, if not entirely, paralysed ; which seems to indicate that a few fibres of the nerves for the blood-vessels of a part can supply the place of the rest more perfectly than is the case with the ordinary nerves of sensation and motion. This peculiarity of the 'vaso-motor' nerves is more strikingly illustrated by the first experiment mentioned in this paper[2], in which it may be remembered that the arteries of the webs completely recovered their usual powers of varying their calibre within half an hour after division of the sciatic, although this is an operation which abolishes for days at least all sensation and voluntary motion in the leg. I have since seen yet more remarkable instances of the same thing. On October 10, 1857, with the view of investigating the nature of the control exercised by the nervous system over the actions of the pigment-cells,[3] I divided all the soft parts in the middle of the thigh of a frog, except the main artery and vein. The first effect upon the arteries was full dilatation ; but about twenty-four hours later they were again of moderate size, while the circulation was still active. After the death of the animal, I examined with the microscope the coats of the artery and vein, and also the periosteum, together with a very slight amount of muscular tissue adhering to it, but could detect no nerves in any of them, although from the method of examination I could hardly have missed branches containing more than very few nerve-tubes. Comparing the result in this case with the permanent dilatation which always occurred after removal of the spinal cord, so long as the circulation continued active, it was evident that the slender filaments contained in the coats of the vessels, or possibly in the bone, had served as an efficient means of communication between the cerebro-spinal axis and the arteries of the foot.

On the 13th of the same month I repeated the experiment upon another frog, operating in this case upon both thighs. In the first place, I divided thoroughly all the soft parts except the artery, vein and nerve, the circulation remaining unaffected. The nerves were then successively cut, full dilatation of the arteries and rapid flow through the capillaries being the immediate result. An hour and a half later, however, the flow was observed to be less rapid, no

[1] Vide pp. 30, 31. [2] Vide p. 29.

[3] Further information regarding this experiment, as respects the pigmentary system, will be found in the next paper (p. 48 of this volume).

doubt in consequence of slight contraction of the arteries, one of which, in the left foot, measured 3° by micrometer, and after sixteen hours more they were both moderate and variable in calibre in both feet ; that in the left limb before noted now changing between $1\frac{1}{2}$° and 2°, and a principal artery in the right foot between 1° and $1\frac{1}{2}$°. The circulation meanwhile continued active, and remained so more than twelve hours longer ; from which circumstance as well as from the normal appearance of the contractions, it was evident that the arteries were still under the control of the cord ; and I may add, that in another animal in which the same operation was performed upon the thigh after removal of the brain and cord, the arteries remained of full size and without variation for thirty-four hours, after which circulation ceased.

From these facts it appears that there exists a very remarkable provision for ensuring the proper regulation of the arterial calibre in a part in spite of almost complete division of the nerves connecting the vessels with the nervous centre which presides over their contractions. It has been shown by recent discovery that sensation and voluntary motion are abolished in parts whose nerves have been divided, until repair has been effected by a process of fresh formation of the nerve-fibres. But the control of the flow of the nutrient fluid is not allowed to be interrupted in this manner, but continues to be exercised more or less perfectly, notwithstanding nearly absolute severance of nervous connexion.

Allusion has been more than once made to the circumstance that arteries do not dilate so fully when the heart is very feeble as when it is in powerful action. This was strikingly illustrated in the case of the frog which was the subject of operation on April 16, 1857. Immediately after the experiments recorded at p. 33, the heart having ceased to cause movement of blood in the web, I induced complete constriction of the arteries by irritating with a needle the posterior part of the cord, and then thoroughly cleared the spinal canal of its contents. The artery under special observation did not, however, become dilated to a greater diameter than $1\frac{1}{2}$°, although during the earlier experiments, when the heart was acting vigorously, it had been observed to attain sometimes a calibre of 3°. The heart never recovered its power, and the vessel maintained this medium width as long as I continued to examine the animal, namely, three hours.

From this and other similar observations, I infer that full dilatation of the arteries is a merely passive phenomenon as respects the parietes of the vessels. Contraction is effected by the muscular fibre-cells of their circular coat, on the relaxation of which the elasticity of the arteries tends to make them expand to a certain degree, beyond which they do not dilate, except in so far as they are distended by the blood.

It was observed by Wharton Jones,[1] that section of the sciatic nerve in the thigh of a frog was followed after a time by oedema of the limb and exfoliation of the epidermis. If this were dependent on the dilatation of the arteries produced by the division of the nerve, the fact would have a very important bearing upon the cause of inflammatory effusion. I find, however, that neither oedema nor exfoliation results from permanent full dilatation produced by operations upon the cord or the roots of the spinal nerves; while, on the contrary, both took place in the case of division of the sciatic, given in the early part of this paper, in which it will be remembered that the arteries recovered their contractility completely within half an hour, and presented, during the next twenty-four hours, precisely similar appearances with those in the other foot. Hence it is evident that the phenomena in question are not due to vascular relaxation, but to some other circumstances attending the operation performed upon the thigh.

It remains to be added, that, in a healthy state of the web, no change in the properties of the blood was ever observed to accompany the constriction of the arteries on irritation of the cord, or the dilatation which followed the destruction of the nervous centre. The exsanguine condition of the web in the former case, and the turgid state of the vessels in the latter, were simply the effects of the variations of calibre in the arteries, the blood flowing more freely in proportion to their width.[2]

To sum up the principal results of this inquiry, it appears—

1st. That, of the nervous centres usually recognized, the cerebro-spinal axis is the only part which regulates the contractions of the arteries of the webs; this function being apparently exercised by the whole length of the cord and the posterior part of the brain, operating through fibres which arise from the same region of the cord as do those through which sensation and motion are effected in the hind legs.

2nd. That there exists within the limb some means, probably ganglionic, by virtue of which the fibre-cells of the circular coat of the arteries may contract in concert with each other, independently of any ganglia contained in the trunk.

And 3rd, that the local co-ordinating apparatus, though capable of independent action in special conditions of direct irritation, is, under ordinary circumstances, in strict subordination to the spinal system; while a remarkable provision exists for the maintenance of this control, notwithstanding almost complete severance of nervous connexion between the cord and the limb.

[1] *Medico-Chir. Trans.*, loc. cit.

[2] The subject of the effect of variations in the calibre of the arteries upon the flow through the capillaries, will be found fully discussed in the paper 'On the Early Stages of Inflammation' (reprinted in this volume, p. 209).

ON THE CUTANEOUS PIGMENTARY SYSTEM OF THE FROG

[*Philosophical Transactions*, Part II for 1858, p. 627.

Received June 18—Read June 18, 1857.[1]

The fact that the skin of the frog is capable of varying in colour, has been for some years known to German naturalists. The first account of the mechanism by which these changes are effected, appears to have been given by Professor Brücke, of Vienna, in 1852,[2] and the subject has since been very carefully investigated by Dr. von Wittich of Königsberg,[3] and Dr. E. Harless of Munich.[4] All these observers describe the dark pigment as contained in stellate cells, each composed of a central part or body and several tubular offsets, which, subdividing minutely and anastomosing freely with one another and also with those of neighbouring cells, constitute a delicate network in the substance of the true skin. They describe the dark contents as sometimes concentrated in the bodies of the cells, at other times diffused throughout the branching processes, the skin of the creature being pale in the former case and dark in the latter. In the tree-frog the change from a dark to a pale state of the body generally was induced by bringing the creature into a bright light, by psychical excitement (as was supposed [5]), or by galvanizing the spinal cord; and a similar effect was produced on a particular portion of the surface by irritating it mechanically, or with oil of turpentine, or by galvanism applied either directly to the part, or through branches of nerves leading to it. After the source of irritation was removed, the skin returned somewhat slowly to its former colour; and von Wittich noticed that when the paleness produced by direct irritation had passed off, the tint became deeper in the irritated spot

[1] During the time that has elapsed between the reading of this paper and its publication, several new observations have been made, which it has been thought best to introduce into the text, distinguished by date or footnote from the matter of the original manuscript.

[2] 'Untersuchungen über den Farbenwechsel des africanischen Chamaeleons,' *iv. Band der mathemat.-naturwissenschaftl. Classe der Kaiserl. Acad. d. Wissensch. Wien.* This paper I have not yet had an opportunity of consulting.

[3] Müller's *Archiv*, 1854.

[4] *Zeitschrift für wissenschaftliche Zoologie*, vol. v, 1854.

[5] This rests on the authority of von Wittich; but, for anything stated to the contrary in his paper, the effects ascribed to psychical excitement may have been connected with the efforts of the creature in struggling, independently of any emotional change.

than elsewhere. The esculent frog exhibited similar phenomena, but was less sensitive. The concentrated state of the pigment is attributed by all the observers above named to contraction of the cells, while the diffused condition is supposed due to their relaxation. The contents of the cells are described as dark granules suspended in a fluid; and both von Wittich and Harless have distinctly seen the granules rolling along in the offsets during the process of concentration. All the authorities agree in the opinion that the fluid and granules move together from one part of the cell to another, the offsets being supposed empty of both when the pigment is accumulated in the body of the cell.[1]

In some respects the above description agrees with my own experience of the common frog of this country (*Rana temporaria*). I find that this well-known animal exhibits changes of hue almost as great as those of the chameleon, every specimen being capable of varying from a very pale to a very dark colour, the former being generally greenish yellow, but in some varieties reddish; and the latter brownish black, or sometimes coal black; while between these extremes any intermediate shade may be assumed. The depth of tint is generally proportioned to that of surrounding objects: thus a frog caught in a recess in a black rock was itself almost black; but after it had been kept for about an hour on white flagstones in the sun, was found to be dusky yellow, with dark spots here and there. It was then placed again in the hollow of the rock, and in a quarter of an hour had resumed its former darkness. These effects are independent of changes of temperature; for similar results may be obtained by placing a frog alternately in a vessel from which luminous rays are excluded, and in a white earthen jar covered with glass, in the same situation. Different examples, however, differ much in their sensitiveness to light. A violent struggle on the part of the animal is often followed by a speedy alteration from a dark to a pale state of the skin. It seems very doubtful whether psychical excitement has anything to do with this occurrence, any more than with the arterial contraction which invariably takes place under

[1] From the way in which von Wittich alludes to Brücke's description, it is clear that the latter supposed the cells to be contractile. Von Wittich himself in his first paper speaks of the movement of the pigment induced by galvanism as 'satisfactorily' showing 'that the stellate pigment-cells are contractile'. In his second paper (vide Müller's *Archiv*, 1854, p. 263), he expresses some doubt regarding the contractility of the *cell-wall*, but clearly speaks of the contents (fluid and granules) as moving together. Harless, after describing 'the rolling of the pigment-molecules towards the centre of the cell', goes on to say, 'that this rolling may be possible, there must be a fluid in the cells and offsets, *to which* the molecules owe their movement.' He takes it for granted that the movement of the fluid must be due to some contractile agency, and as he finds no apparatus of this nature around the cells, and as the unstriped muscular fibres of the skin have no special relation to them, he infers that the cell-wall is itself contractile.

such circumstances. Neither oil of turpentine nor galvanism, when applied to the integument, produces, so far as I have seen, any effect upon its colour; our species being little influenced in this respect by direct irritation. I have, however, frequently observed, after forcibly pinching a dark web, that a pale ring, about one-sixteenth of an inch in breadth, has formed around the area so treated; but this was very slow in appearing, being first noticed from half an hour to an hour after the pinch was given.

The webs of the hind feet, examined under a low power of the microscope, exhibit differences in the distribution of the dark pigment[1] according to the tint of the skin, such as will be understood by referring to Plate III (p. 68), where Fig. 1 is from a dark portion of web, and Fig. 2 from a pale part in the same animal. In Fig. 2 the colouring matter is seen to be collected in black spots of irregular angular shape. This, however, is not the state which exists when the colour is palest, for then the masses of pigment are in the form of round dots, as in the part to the right in Fig. 1, Plate V (p. 274). Neither does Fig. 1 of Plate III give the condition met with when the skin is darkest, in which case all that meets the eye on superficial observation is a reticular appearance, such as is represented in the stripe down the middle of Fig. 1, Plate V, and in the lower part of Fig. 2 in the same Plate. When the colour of the integument is about medium, the pigment is disposed in a truly stellate manner, as on the left side of Fig. 1, Plate V. It may be convenient for the purposes of description, to designate these various states as respectively the dotted, angular, stellate, and reticular conditions of the pigment.

When a higher magnifying power is applied in an extremely dark state of the skin, the chromatophorous cells, for such they seem to be, appear as depicted in Plate III, Fig. 3, where two of them are given, along with an adjacent capillary distended with blood-corpuscles. Each cell consists of a somewhat flattened central part with several irregular offsets, of considerable diameter near the central part, but speedily breaking up into small branches. The ultimate ramifications, some of which are of extreme minuteness, anastomose freely with one another and with those of neighbouring cells, constituting a very delicate and close-meshed network, which pervades the whole thickness of the

[1] Other kinds of pigment are also present in the skin of the common frog, generally of yellow colour, but sometimes red. My attention has not been much directed to these, but I have noticed that they are contained in receptacles of the same general form and structure as those which hold dark pigment; and on one occasion, since the reading of the paper, I observed the colouring matter disposed in a stellate manner with complex ramifications in one part of a web, and in another part collected into round spots; implying that these cells possess the functions of concentration and diffusion of the pigment. They do not, however, always act in harmony with the dark cells; and it is probably through their agency that changes in tint, such as I have seen to occur in one and the same frog, independent of mere lightness and darkness of shade, are produced.

true skin, and especially follows the course of the blood-vessels, entering into the composition of the cellular coat of the arteries and veins, and twining about the capillaries in a very remarkable manner. The walls of these cells and of their tubular offsets appear to be extremely delicate, and some attempts which I have made to isolate them from surrounding tissues have barely served to demonstrate their existence. The cells vary considerably in dimensions according to the size of the animal; thus, those in Figs. 8, 9, and 10, which are from young frogs, though magnified 500 diameters, show in the drawing even smaller than those in Fig. 3, magnified only 250 times, the latter being from a full-grown specimen. In an average full-sized cell of a large frog, the middle portion was found to measure 1–330th of an inch in length by 1–670th of an inch in breadth, and 1–1500th of an inch in thickness. The last-named dimension was obtained by carrying the focus of an object-glass of high power, from the most superficial to the deepest part by the screw for giving slow motion, and reading off on its graduated circle the number of divisions traversed, these having a known proportion to the depth measured. Opportunities for testing the correctness of this measurement were presented by other cells which lay edgewise, so that their thickness could be observed directly.

Perhaps the strongest argument in favour of the cellular nature of these receptacles of colouring matter is afforded by the universal presence of a nucleus in the central cavity of each. In large frogs it is often difficult or impossible to discover clear evidence of it, but in small ones, in which the web is much thinner and its constituent parts therefore capable of clearer definition with the microscope, it can be quite distinctly seen in the reticular condition of the pigment. Its form and relations may be gathered from Figs. 8, 9, and 10. In 8 and 10 the bodies of the cells are viewed on the flat, and the nucleus appears as an oval colourless body, about 1–2500th of an inch long by 1–3300th of an inch broad. In Fig. 9 the body of the cell is seen edgewise applied to the wall of a capillary blood-vessel, which is embraced by its processes. The thickness of the nucleus is thus displayed, and is shown to be equal to that of the cell in which it lies, which in fact it causes to bulge slightly, and also nearly as great as the breadth of the nucleus in Figs. 8 and 10. In the cell of Fig. 10, the thickness of the nucleus, measured in the manner above described, was found about equal to its breadth. The nucleus in Fig. 8 is not centrally placed in the body of the cell, and I have in some other cases seen it still more eccentric.[1]

The contents of these cells are very minute dark granules or molecules sus-

[1] The precise relations and dimensions of the nucleus have been ascertained subsequently to the reading of the paper.

pended in a colourless fluid, in which I have often seen them moving freely: when in considerable mass they produce a jet-black appearance, but exhibit a brown tint when present only in small quantity.

When the skin of the animal is very pale, the colouring matter is all accumulated in the central parts of the cells. With regard to the method in which this change is effected, I am compelled to differ altogether from the before-mentioned authorities, who suppose that the granules and fluid are together forced by contraction from the processes into the bodies of the cells. They seem to take it for granted that the depth of tint of any one part of a cell depends simply upon the bulk of the contents situated there, and the consequent thickness of the coloured medium through which the light passes before reaching the eye. This, however, is by no means the case, as may be seen by referring again to Plate III, Fig. 3. The pigment is there represented fully diffused through the ramifications of the offsets, and some of the smallest of these are darker than the bodies of the cells and the adjoining broad parts of the processes; yet the former are far from being thicker than the latter: on the contrary, some of the branches, though conspicuous for their blackness, appear but as delicate lines which can be seen only at one focus when a glass of very high power is employed; while the bodies of the cells, as above mentioned, possess considerable thickness, and the processes are not flat, but subcylindrical. But the differences in tint are sufficiently accounted for by the circumstance that in the dark branches the colouring particles are closely packed together, whereas in the bodies of the cells and the paler parts of the offsets, the individual granules are separated from one another by considerable colourless intervals. Hence it is clear that the degree of darkness of any part of a cell does not depend so much on the bulk of its contents in the aggregate, as on the proportion which the pigment molecules in it bear to the fluid in which they are suspended.

If the whole contents of the processes were forced into the central parts during concentration of the pigment, and driven back again during diffusion, the bodies of the cells would be subject to great variations in capacity, becoming turgid in concentration and collapsed in diffusion; and the bulk of the central coloured mass would be great in the former case, but small in the latter. The very reverse, however, really takes place. Fig. 6 represents the appearance of the pigment in a concentrated condition, in one of the same cells which in Fig. 3 show it in full diffusion. During the time in which this change took place, the adjacent capillary had shrunk to about half its former size, but it will be recognized by its general form, and will indicate which of the two cells is that under consideration. Both the figures were drawn on the same scale with the camera lucida,[1] so that accuracy of proportion is ensured. The circular black mass into which the colouring matter is now all collected, measures less across than either the length or breadth of the body of the cell in the diffused state of the pigment. Further, the mass is not spherical, but of flattened form, and its thickness is only about that of the central part of the cell in diffusion. This we know from the appearances presented by the spots of concentrated pigment in other cells seen edgewise, as is the case with some in Fig. 7, which represents the outline of the wall of a large blood-vessel, and the pigment contained in its external coat in nearly complete concentration. Hence it appears that all the pigment-granules contained in the body of the cell and the minutely ramifying processes in the diffused state, have been brought together into a space considerably less than was then occupied by the pale contents of the body of the cell alone. The coloured particles have been concentrated into a dense disciform mass, but the fluid in which they were suspended has been left behind.

Fig. 4 shows the pigment in the same cells as Fig. 3 in an intermediate stage, in which the process of concentration is about half accomplished ; the upper one being in the condition which would appear stellate under a low magnifying power. The greater part of the pigment is collected in the bodies of the cells, especially towards their central parts : in the middle of each dark mass, however, is a pale spot, doubtless due to the circumstance of the granules not having yet insinuated themselves between the cell-wall and the nucleus, which, as shown above, probably lies in contact with it. This appearance of pale central points was very general in the web at the time when Fig. 4 was drawn, but gradually disappeared as the aggregation of the pigment-molecules proceeded, and does not exist in Fig. 5, which represents the lower of the two cells in a more advanced state of concentration. The remote branches of the processes were then for the most part invisible, and those which did appear were generally pale, instead of dark, as they had been during full diffusion. This difference does not depend on contraction of the branches, but on the granules being absent from them, or sparsely scattered instead of closely packed ; and I have often ascertained from some granules remaining widely separated in a process, that it was of large calibre, though, without careful searching, it would have seemed invisible Even in Fig. 6 concentration is not represented absolutely perfect ; for a few molecules are to be observed near the black mass in the more circumferential parts of the body of the cell. The extreme delicacy of the cell-wall makes it very difficult to trace it among the surrounding tissues, and I have not attempted

[1] All the drawings in the plate which accompany this paper were made with the assistance of this very valuable instrument.

to give it in these figures, which, it must be clearly borne in mind, represent only the colouring matter. The external parts of the body of the cell and the principal processes may, however, be sometimes discovered, though perfectly colourless in consequence of concentration: they are then found to be of the usual dimensions met with in full diffusion, showing that they are still full of fluid though destitute of granules. In fact the only change of form to which the cells appear liable is a slight bulging of the central part at the seat of the black mass in the concentrated state, which I have detected in some cases by camera-lucida sketching, and which is consistent with the separation of the cell-wall from the nucleus, implied by the ultimate disappearance of the central pale points of Fig. 4.

The movement of the granules towards the centres of the cells may be seen without any great difficulty. The death of a healthy frog is always followed by complete concentration of the pigment for a time, however much diffused it may have previously been, and the process taking place gradually, its progress can be observed. If a frog with the skin dark, and the pigment therefore diffused, be killed and the web examined soon with a good glass of high power, the granules may be seen distinctly moving along the offsets of each cell to join the dark mass which is becoming accumulated in the central part. If the process is going on languidly, the individual molecules advance slowly with slightly dancing movements, indicating that they are free in the fluid and not confined in any way to the cell-wall. If concentration is taking place more speedily, the granules rush along so quickly that no time is allowed for observing their molecular movements, and often their motion is so rapid as to elude the eye altogether. In one instance a large-sized offset, which at first contained abundance of pigment, became gradually cleared in this way of its colouring matter without any change in its dimensions, till it was almost invisible on account of the very small number of molecules remaining in it.

It is thus a matter of direct observation, that the pigment-granules move along into the bodies of the cells during concentration, and leave colourless fluid behind them in the processes. It is clear that their motion cannot be explained by currents in the fluid; for streams proceeding towards the centre of a cell would necessarily be accompanied by a returning flow in the opposite direction, which would carry the pigment with it unless the molecules had a special tendency towards the centre. The circular form assumed by the mass of pigment when concentration is complete is strongly suggestive of a central attractive force acting on the granules. The occurrence of the central pale points, which are represented in Fig. 4, showing that the nucleus was there in the middle of the concentrating pigment, led me at first to suppose that this body was the attractive agent.[1] I afterwards took pains to ascertain whether the nucleus always has this relation to the mass, and found that such is not the case. On October 22, 1857, I watched three adjacent cells during the process of post mortem concentration ; in two of them the nucleus ultimately projected by about a quarter of its length at one side from the black spot, while in the other cell the aggregated molecules covered only one-third of the nucleus, so that *no part* of that body lay in the middle of the mass. The point to which the granules appear to have a special tendency is the middle of the body of the cell, which seems always to correspond with the centre of the disc of molecules, whereas the nucleus is often eccentrically placed in the cell.

The diffusion of the molecules is not merely a passive result of the cessation of concentration, as has been hitherto supposed. In watching closely the occurrence of the phenomenon, I have seen [2] the granules start off suddenly from the central mass, with a velocity which implied that they were under the influence of forces very different from those which cause molecular movements in them when shed from their containing cells. That the process requires the vital forces of the cells to be in full operation is also proved by the fact that any agency, such as a galvanic shock, which temporarily paralyses their functions, arrests diffusion as well as concentration ; whereas, if the former were merely passive, it would take place as soon as the concentrating power was set at rest.

I have already pointed out the sparsely scattered state of the granules in the central receptacles, compared with their accumulation in the branches of the offsets, in the fully diffused state shown in Fig. 3. This contrast is sometimes much more striking, so that the bodies of the cells are almost colourless, and require some experience with the tissue in order to detect them. This indicates a special tendency on the part of the granules to leave the middle of the cell. Yet to however great a degree diffusion be carried, there always remain some molecules in the body of the cell uniformly distributed throughout its thickness and not attached to the parietes, as they would have been had their dispersion been caused by attraction on the part of the cell-wall. This disposition of the granules, which obtains even in the immediate vicinity of the nucleus, appears also distinct evidence against the operation of a central repulsive force ; for this would render the body and the adjoining parts of the processes as clear of pigment as the remote branches are made in concentration.

[1] This was the view expressed in the paper as it was read.
[2] This observation was made after the reading of the paper.

The hypothesis which would seem most consistent with the appearances described, is that of a mutual repulsion on the part of the pigment-granules, induced by some agency strongest at the centre of the cell and feeble in the remotest branches of the offsets.

On October 27, 1857, I was observing a cell in which post mortem concentration had occurred, the pigment being in the angular condition. At one of the angles movements of the granules were going on, of which I will content myself with giving two examples. At one time a number of molecules started off together with great rapidity from the black mass, but stopped after having proceeded a certain distance, some of them remaining in their new position, while others returned at various rates towards the centre. At another time an individual granule moved slowly away for a little space, and then came back by a circuitous route to a different part of the mass from that which it had left. What I then saw has led me to believe that the movements of the pigment-molecules are of a complex character that will perhaps never be fully explained. In the meantime it is clear that concentration and diffusion are both active vital functions, and that both imply peculiar relations of the centre of each cell to the pigment-molecules, as distinguished from the fluid in which they are suspended.

These conclusions invest the pigmentary changes with deep physiological interest. In the movements of the granules towards and from the centres of their containing cells, we now have ocular demonstration that a particular kind of material may have impressed upon it by vital action, independently of muscular contraction or ciliary motion, tendencies to rush energetically to or from certain fixed points in the tissues, through distances equal to nearly twice the thickness of a villus of the human intestine, and several times greater than the average breadth of a human capillary interspace. Whether we be able to explain the means by which such results are accomplished or not, it is obvious that forces of similar powers and range of operation, if suitably modified according to the circumstances of each case, would be more than adequate to cause the passage of particles of fat from the cavity of the intestine into the central lacteals of the villi, or the transit of the material required for a particular secretion or act of nutrition out of a capillary into a neighbouring gland cell or other portion of tissue; and, again, for the discharge of an elaborated product of secretion into a duct, or the return of waste matter into the blood-vessels or lymphatics. We thus obtain a basis of fact for what has hitherto been merely conjectural, in the explanation of the processes of absorption, secretion, and nutrition generally.

The functions of the pigment-cells are under the control of the nervous system,[1] as is evident from the effects produced on the colour of the skin by a struggle on the part of the animal.

Much attention has been devoted by von Wittich to the inquiry, by what ganglionic centres this control is exercised. He found that division of the sciatic nerve in the thigh, or of cutaneous branches in the dorsal region, did not prevent the parts of the skin supplied by them varying in colour along with the rest of the body under the influence of light; and, supposing that in such operations all connexion was severed between the portions of integument concerned and the central organs of the nervous system, he inferred that the pigmentary changes induced by light were effected independently of either the cerebro-spinal axis or the usually recognized sympathetic ganglia. He nevertheless regarded such variations as probably reflex in their nature, and attributed them to a peripheral ganglionic apparatus in the skin itself; and this opinion appeared confirmed by the circumstance that direct irritation operated in the same manner upon the colour of a detached piece of integument as upon that of the living animal. At the same time, as he observed paleness of tint to result from irritation of the cord, or of the nerves distributed to a particular part of the surface, he concluded that the spinal system was also capable of acting on the pigment-cells, and so accounted for the supposed influence of psychical excitement upon the tint of the skin. Thus, according to his view, the cutaneous pigmentary system was circumstanced like the heart or intestines, which, though possessing the faculty of independent action by virtue of their intrinsic ganglia, may also have their movements affected by mental emotion.[2]

In the course of some experiments performed in April 1857, with reference to the influence exerted by the cord upon the calibre of the arteries, I noticed on two occasions that partial division of the roots of the nerves for one of the hind legs within the spinal canal was immediately followed by increased paleness of the limb, of transient character, after which the leg assumed precisely the same colour as the other, this result being in accordance with von Wittich's description. But I further observed in two cases in which such operations had been performed, that when a considerable time had elaspsed, viz. nine hours in one instance and two days in the other, the limb whose nerves had been cut was decidedly darker than the rest of the body. Similar results were once obtained from the division of the sciatic nerve in the thigh. When the operation was performed, viz. at 4^{h} 30^{m} p.m. on April 4, 1857, the pigment was in

[1] The part of the paper devoted to this branch of the subject has been entirely rewritten; and the dates in the text imply that most of the observations with reference to it have been made since the reading of the manuscript before the Society.

[2] Vide Müller's *Archiv*, loc. cit., p. 56.

the stellate condition in the webs, the tint of the skin being moderately dark ; and this state of things continued unchanged in both limbs for the next six hours. On the following day, however, the leg operated on was seen to be very dark, and the pigment in its webs was reticular ; while in the rest of the body the colour remained as before, and the pigment was still stellate. This striking contrast continued unaltered for two days, when it was destroyed by the body generally assuming the darkest possible tint.

The diffusion of the pigment in consequence of division of nerves appeared to be the counterpart of the concentration by their irritation, and it seemed probable that the want of constancy in the results in the former case was caused, like the variable amount and duration of arterial dilatation after such operations,[1] by the place of the divided trunks being supplied by other branches ; and that, if the nerves of a limb were all completely severed, diffusion would necessarily take place. With the view of testing the truth of this idea, the following experiment was performed. In the afternoon of October 10, 1857, I divided in a pale frog all the soft parts in the middle of the right thigh, except the femoral artery and vein and the sciatic nerve ; and late in the evening, having ascertained that the circulation was going on freely in the webs, I cut the nerve also, no effect having been hitherto produced upon the colour of the limb. Next morning the body generally was still pale, but the right leg was black from the wound downwards. The same remarkable appearance continued till the evening, when circulation ceased in the limb. On the 13th I performed the same experiment upon both thighs of another large pale frog, leaving the sciatic trunks entire in the first instance, until I had ascertained that the circulation in the feet had not been interfered with. Three hours after this had been done I divided the nerve in the left thigh, and in about forty minutes observed that the leg was decidedly darker below the seat of operation. After another hour I found the pigment stellate in the left webs, whereas it was in the dotted condition in the right foot. I then cut the nerve in the right limb, and within a quarter of an hour the leg was already considerably darker below the wound, and the pigment in the webs had become stellate. Next morning the body was still pale, but the legs were very dark, and they continued to deepen in tint, although the animal was kept in a white earthen jar covered with glass in a bright light, till at about 3 p.m. they were almost absolutely black, while the pigment was diffused in the webs to the extremest degree, the body meanwhile and the upper parts of the thighs retaining their former light colour. The tint of the legs remained unaltered till the death of the animal, which took place several hours later.

[1] See p. 31.

The natural interpretation of these results appeared to be, that there exists a constant tendency to diffusion of the pigment in a limb so soon as it is liberated from the influence of the usually recognized nervous centres. It afterwards occurred to me, that if this were really true, diffusion of the pigment might, by proper management, be observed in an amputated limb before the supervention of the tendency to post mortem concentration: for I knew, from reasons to be mentioned hereafter, that this effect of death depended on the cessation of the flow of blood through the vessels, and, from what I had seen of arterial contractions in the frog's web, and vermicular movements of the mammalian intestine from a similar cause, I felt sure that, if the blood were retained within the vessels, the arrest of the circulation could not be instantaneous in its effects upon the pigment, but that some minutes would probably be required to develop them; during which time the diffusion resulting from liberation of the pigment-cells from the influence of the ganglia in the trunk would proceed unchecked. Accordingly, on September 3, 1858, having tied a string tightly round the ankle of a pale frog, I immediately amputated above the ligature, and, avoiding the loss of time involved in tying out the toes, placed the foot at once on a plate of glass with a drop of water, two adjacent toes being kept apart by morsels of moistened lint. Within a minute and a half of the application of the string, the pigment in the web was observed to be in the angular condition, with short simple projecting processes, i.e. approaching stellate, and two minutes later two contiguous cells were sketched in that state. About a minute after this it was evident that diffusion was taking place, and it continued to develop itself during the next ten minutes, at the end of which time the rays of the stellate pigment had shot out complicated offsets. Within the following five minutes, however, it was arrested by post mortem concentration, which gradually carried the pigment back to the angular state. This experiment, therefore, furnished confirmation of the view, that, in the ordinary circumstances of the animal, the influence of the central organs of the nervous system is required for the maintenance as well as the development of concentration of the pigment in the limbs.

Supposing this to be established, it would follow that the accommodation of the tint of the skin to that of surrounding objects is certainly not the result of direct action of the rays of light upon the pigment-cells, but a reflex phenomenon; and it was an interesting question whether the afferent nerves concerned were the optic pair, or branches in the skin sensitive to luminous impressions. With a view to determining this point, I completely removed the eyes of a pale frog on September 13, 1858, at 1 p.m., and then placed it in a dark cupboard. During the first hour after the operation it became even paler than before, no doubt in consequence of the injury which had been inflicted,[1] assuming apparently the lightest possible shade; and this continued with very little change till night, although the animal was still kept in the dark. Next morning it was decidedly darker, and the tint was still deeper at 2h 25m p.m. The glass containing the frog was now placed in a bright light, and surrounded on all sides by white objects; but this change produced no difference in the colour of the skin, which continued till 7h 30m p.m. of a peculiar dingy hue. It was then put back into the dark place, and at 11h 40m p.m. was still exactly the same. On the following day, at 8 a.m., the animal seemed a little paler, and was even lighter at 10 a.m., though still in the dark; so that it was evident that no difference whatever was produced upon its colour by admission or exclusion of light. But that the nervous system generally was in a state quite disposed for acting upon the pigment-cells when subjected to appropriate irritation, was shown by the following circumstances. At the hour last mentioned, the animal, having escaped from the vessel in which it was contained, struggled violently during my attempts to secure it, and in the short time thus occupied changed to almost the palest possible tint. It was then placed at once in the bright light, as before, but, in spite of this, was within ten minutes already decidedly darker, and, half an hour later, was almost coal black, though still subject to the full influence of white light. Just after this observation was made, the frog again escaped, and having again struggled considerably before it was replaced in the glass, it was seen to be within four minutes as pale as when first observed in the morning, but after the lapse of another half hour it was again almost as dark as ever, and continued so till 2h 30m p.m., though all the while exposed to the same light. The observations were continued for two more days, during which period the same complete indifference to the brightness or obscurity of surrounding objects was still evinced.

These facts indicated pretty clearly that the eyes are the only channels through which the rays of light gain access to the nervous system so as to induce changes of colour in the skin. But for the sake of confirmation I thought it worth while to perform the following experiment. Two very dark frogs having been obtained, I put a hood of black cloth on the head of one of them, leaving the body and limbs uncovered, an aperture being made in the cloth below the throat for the purposes of respiration, and then placed them both in the same glass vessel exposed to white light. The struggles of the animal while the covering was being adapted and secured had the effect of making it grow much paler, so that it was of about medium tint when introduced into the

[1] Probably from the irritation of the optic nerves.

glass ; while the other, which was from the first the darker of the two, still retained its original coal-black appearance. Half an hour after this had been done, the contrast between them was much diminished, partly in consequence of the dark one having become slightly paler, but much more from the paler having grown darker. After another half hour they were of precisely the same colour, and when another similar period had elapsed, that which was the darker to begin with was distinctly the paler of the two, being much lighter than at first, though still considerably darker than medium. A hood was now placed upon this animal, and that upon the other was removed, and both were replaced in the same light as before. This procedure occupied about ten minutes, and within seven minutes of its completion the creature which had the head uncovered was already the paler of the two, having grown decidedly lighter in colour ; while that on which the cap had been last placed seemed somewhat darker ; and after another hour, while the latter was still of much the same dark shade, the former, with the head exposed, was very much paler, being about midway between the medium and the palest possible tint. An experiment of the same kind was performed upon another pair of frogs with very similar results, the details of which it is not necessary to mention. I afterwards found that the presence of the hood tends to check diffusion, or even in some cases to give rise to concentration of the pigment, probably by making the animal struggle to throw it off ; so that in one instance a frog which was put in a perfectly dark place, immediately after the cap had been put on, grew much paler in the course of two hours. This circumstance prevents the skin from becoming as dark on the application of the hood as it would do if the head could be covered without exciting the animal. This, however, only renders the facts above mentioned more striking, so that they afford of themselves sufficient proof that the direct action of light upon the integument is incapable of affecting the pigmentary functions ; and thus the conclusion before arrived at receives complete confirmation from these experiments.

There is of course nothing new in the fact that other functions besides vision may be excited in a reflex manner through the optic nerves ; the contraction of the pupil, and the sneezing experienced by many persons on coming suddenly into bright sunshine, being well-known examples of such phenomena. On the other hand, the view that the cutaneous nerves are sensitive to luminous impressions was destitute of any support from analogy.[1]

[1] In the chameleon, a part exposed to the sun becomes dark, while the rest of the body remains unaffected. I have little doubt, however, that this is due to the calorific, not the luminous rays. That heat does produce such an effect was lately demonstrated to me by Professor Goodsir upon a living chameleon, which, when held in broad daylight before a dull-red fire for a short time, grew much darker on the side that was warmed, but retained elsewhere its former pale green colour.

From the part taken by the second pair of nerves in bringing about the changes in the tint of the skin under the influence of light, and also from the darkening of the hind legs observed to occur after dividing within the canal the roots of the branches which supply them,[1] we learn that the cerebro-spinal axis is chiefly, if not exclusively, concerned in regulating the functions of the pigment-cells. Considering that those functions have probably a close affinity with the processes of secretion and nutrition, it is interesting to find that they are thus subject to the control of the spinal system.

The circumstance before alluded to, that a dark frog always becomes pale after death, is mentioned both by von Wittich and Harless, but without any discussion of its cause. This post mortem concentration takes place in a limb in spite of amputation, and therefore cannot be due to the agency of any ganglia contained in the head or trunk. Neither can it be the result of failure in action on the part of such ganglia ; for if the circulation be artificially arrested in a part of a living frog without interfering with the nerves leading to it, a similar change in the pigment to that which results from death comes on before the nerves have become, so far as we can judge, at all impaired in their functions. This was proved by the following experiment :—On June 7, 1858, having tied the right femoral artery of a moderately dark frog in the middle of its course, I divided it below the ligature, and also cut through, in the same situation, all the soft parts of the thigh except the sciatic nerve with a little adherent muscle. The operation was completed at noon, when the animal was put into a dark place ; and at 1^{h} 40^{m} p.m. the body generally was darker, but the right leg from the wound downwards was decidedly paler than before ; the animal, however, still moved it freely. At 6^{h} 20^{m} p.m. the general surface was as dark as ever, but the right foot presented the extreme degree of pallor ; yet the creature still moved the leg both spontaneously and when the toes were pinched, showing that the motor and sensor nerves retained their functions. Sensation, however, was not so acute as in the left foot ; in the latter a touch sufficed to induce movements in the body generally, whereas in the former a pinch was necessary to produce the same effect. At 10^{h} 15^{m} p.m. the same contrast in colour continued, but no movement could be induced in any manner in the pale limb, although obscure indications of a certain amount of sensibility remaining in it were still elicited by forcible pinching.

In this case, concentration of the pigment came on in the limb in consequence of arrest of the circulation through it, several hours before its nerves concerned in sensation and motion had lost their powers, and therefore at a time when we cannot doubt that the ganglia in the trunk had full opportunity

[1] See p. 57.

for acting on the pigment-cells, which, as we know from experiments before mentioned, are capable of being influenced through the sciatic trunk. Hence it appears that post mortem concentration is the result of the cessation of the flow of the blood through the vessels, and that it is a purely local phenomenon developed in some manner quite independent of the central organs of the nervous system.

The period at which it occurs varies a good deal in different cases. This seems to depend partly upon whether the blood is retained in the vessels or not. Thus in one instance in which a piece of web was cut out, so as to ensure complete escape of the vital fluid, the process was already considerably advanced within nine minutes ; whereas in the case above related, in which the blood was retained in the limb by a ligature, concentration did not commence till full a quarter of an hour after amputation. The season of the year also seems to have a great effect. In a cold room, in the depth of winter, I have known some hours elapse before the pigment began to change in an amputated limb : this is probably owing to greater languor in all the vital processes during the period in which the creature naturally hibernates.

The dead frog, if previously healthy, assumes after a while a nearly uniform pale colour, concentration being carried to the extreme degree in all parts. It does not, however, remain in this condition ; for when a variable time has passed, the skin becomes again somewhat darker, and on microscopic examination the pigment is found pretty uniformly angular or stellate. Nor are these the only changes to which the pigment is liable after death, as I first became aware in April 1858, when examining an amputated limb with reference to the post mortem contractions of the arteries, the blood being retained in the vessels. In that case, after complete concentration followed by slight diffusion had taken place, irregular changes began to appear ; some tracts of the web under observation becoming affected with more or less full diffusion of the pigment, while in others it became more concentrated. Then after the lapse of some hours its state was found reversed, being concentrated in parts where it had been diffused, and vice versa. These curious variations continued till so late as the tenth day after amputation, becoming more frequent after the first few days ; so that sometimes a considerable alteration was observable within half an hour.

These facts appeared to me of great importance, as proving the continuance of vital actions for a much longer time than had been previously supposed possible in a severed portion of the body. They seem also valuable with reference to the influence of the nervous system over the pigmentary functions ; for the circumstance that considerable patches of the web usually had the pigment in the same condition throughout at one time implies that a large number of pigment-cells were acting in concert, and therefore probably under the control of the nervous system, although, as the leg had been amputated, they were of course freed from the influence of the central ganglia. Hence we are led to suspect the existence in the limb of an apparatus, probably ganglionic in structure, co-ordinating the actions of the pigment-cells, just as we know that the muscular contractions in the mammalian intestine are harmonized by a local mechanism of that nature, while we have reason to think that the same thing holds regarding the arteries in the frog's web.[1] Such a view is in accordance with the results of recent anatomical discovery, which has revealed nerve-cells in many parts where their occurrence had not previously been conjectured. But in the absence of more positive evidence, we must be careful not to trust too much to analogy on such a point ; for it by no means necessarily follows, that, even if muscular fibre-cells are incapable of acting in mutual harmony without the aid of the nervous system, the same must be the case with pigment-cells, which, it is to be remarked, resemble ganglion corpuscles in being connected together by anatomosing offsets. The nerve-cells, if such be really the means by which the harmonious actions of the pigment-cells in an amputated limb are induced, must be disseminated among the tissues of the web itself ; for both post mortem concentration and secondary diffusion occur in a piece of web cut out and placed in a drop of water on a plate of glass. This was ascertained on September 4, 1858, in the case already alluded to as an instance of rapid occurrence of concentration. About half an hour after removal from the body, the pigment, previously reticular, was in the dotted state, and three hours later it was found to be again stellate.

The case of the pigment-cells is analogous to that of the arteries in this respect, that, so long as circulation is going on, they are generally in entire subjection to the central ganglia, and act only when stimulated by their influence. But as, in the arteries, it appears to be by the independent action of the local nerves that a contraction caused by direct irritation spreads to a considerable distance from the part operated on, so it is probably by local means that the pallor induced by pinching the web affects a circle of surrounding tissue. If this be true, the case of direct irritation will be an exception to the general rule, that, while circulation continues healthy, concentration always implies the operation of the central organs of the nervous system.

Comparing the changes in the pigment in an amputated limb with those which take place under similar circumstances in the arteries,[2] it appears that

[1] See the preceding paper 'On the Parts of the Nervous System which regulate the Contractions of the Arteries', p. 41. [2] See the preceding paper before referred to, p. 39.

the first effect of removal from the influence of the nervous centres in the head and trunk is arterial relaxation and pigmentary diffusion, followed in a variable time by contraction of the vessels and concentration of the dark molecules, giving place again to relaxation and diffusion, after which succeed irregular alternations of contraction and dilatation in the one case, and of concentration and diffusion in the other. Here, though the vascular and pigmentary changes do not at all correspond with one another in point of time, yet there is an evident parallel between them ; and, admitting that in each case the variations are the result of alternate action and inaction of the appropriate local nervous system, it is evident that concentration of the pigment corresponds to contraction of the muscular fibres of the arteries ; these being both the results of nervous action, while diffusion of the pigment, like arterial relaxation, takes place when the nerves cease to operate. It will be remembered that a similar conclusion was derived from the study of the influence exerted upon the pigment-cells by the central ganglia. Hence it appears that the tendency to diffusion of the pigment-molecules is in constant operation in the cells, but kept in check by an antagonistic concentrating agency varying in obedience to nervous influence.

It is an interesting circumstance, that two functions seemingly so totally distinct as muscular contraction and pigmentary concentration, should both be thrown into a state of activity in consequence of arrest of the circulation. It is to be remembered, however, that there is no evidence that either the involuntary muscular fibre or the pigmentary tissue is directly influenced by the cessation of the flow of blood, the effect being apparently produced through the medium of the local nervous system. This we know with certainty in the case of the post mortem movements of the intestines ; and we have seen reason to think it likely that the same is true regarding the contractions of the arteries after death, and the concentration of the pigment under similar circumstances. It is a curious question how the arrest of the circulation causes these actions of the local nerves. The idea suggested by the facts is that the tissues begin to suffer from the want of fresh supplies of the vital fluid, and resent the injury, as it were, by a struggle.

Rich in results of general physiological interest as the study of the pigmentary system of the frog has proved, it has yielded fruit of not less value in a pathological point of view. Indeed, what induced me to investigate the functions of concentration and diffusion, was the unexpected light thrown upon the nature of inflammation by the effects produced by irritants upon those processes. For information on this subject I beg to refer the reader to my paper 'On the Early Stages of Inflammation'.[1]

[1] See p. 209 of this volume.

The pigmentary system also promises to render good service in toxological inquiry. Hitherto, in experiments performed upon animals with that object, attention has been directed chiefly, if not exclusively, to the effects produced upon the actions of the nervous centres, the nerves and the muscles. In the pigment-cells we have a form of tissue with entirely new functions, which, though apparently allied to the most recondite processes of the animal economy, yet produce very obvious effects, and thus afford great facilities for ascertaining whether or not they have been destroyed by any poison that may have been administered.

An experiment of this kind which I once performed, though with a different object, may be mentioned by way of example. Being desirous of confirming the conclusion to which I had been led by experiments above related, viz. that diffusion always tends to take place when the influence of the nerves is withdrawn from the pigment-cells, it occurred to me that the urari poison might be brought into requisition for that purpose : for it has been shown by Professor Kölliker of Würzburg, that this substance paralyses in the first instance the extremities of the motor nerves without affecting the contractility of the muscular tissue ; and supposing the nerves concerned in regulating the pigmentary changes to be similarly deprived of their powers, while the pigment-cells themselves remained intact, diffusion should take place after exhibition of the drug, provided my view were correct. Accordingly, at $2^{h}\ 10^{m}$ p.m. on December 21, 1857, I introduced beneath the skin of the back of a pale frog a portion of urari extract, for which I was indebted to the kindness of Dr. Christison. At $2^{h}\ 25^{m}$ reflex action was entirely abolished, the creature being to all appearance dead, so far as could be judged by the naked eye, although the microscope showed that circulation continued in the webs. The pigment meanwhile had become stellate, but did not continue in that condition, being, half an hour later, found fully concentrated. Soon after this, however, diffusion again commenced, and continued to advance steadily till circulation ceased early the following morning, at which time the integument was almost black. In the course of a few hours, however, it was brought again back to the palest possible tint by post mortem concentration.

The diffusion which ultimately took place in this case was no doubt due to loss of function on the part of the central ganglia or the nerves connecting them with the pigment-cells. But from the occurrence of concentration half an hour after the faculty for reflex action had ceased, we learn that these nerves, like the intrinsic motor nerves of the heart and intestines, remain unaffected by the urari poison for a considerably longer time than those which excite the contractions of the voluntary muscles. We further learn from the fact that post mortem concentration came on as usual, that the pigment-cells retain their powers, and also their capability of acting in mutual harmony after the rhythmical contractions of the heart have been abolished by this poison.

Such experiments are so readily performed, and the effects produced upon the pigment-cells or the nerves which govern them are so obviously indicated by the changes of colour in the integument, that I venture to recommend this method of investigation to those who are occupied in studying the action of poisons.

PLATE III

illustrates the anatomy and physiology of the cutaneous pigmentary system of the frog.

Figs. 1 and 2 are sketched from webs of different feet of the same animal. The creature was dark when it was killed, but one of the legs afterwards underwent the usual post mortem change to a pale colour, and such was its state when Fig. 2 was drawn. The other limb was deprived of the power of thus altering by immersion for half a minute in chloroform ; and Fig. 1 shows the appearance of the colouring matter in the permanently dark condition of the integument.

Fig. 3 represents two chromatophorous cells with the pigment-granules fully diffused, the animal having been at the time coal-black. The bodies of the cells are seen to be pale, containing chiefly colourless fluid, while some of the finest branches of the offsets are quite black, in consequence of the dark molecules being closely packed together in them. In the same figure a capillary fully distended with blood-corpuscles is also given.

Fig. 4 represents the colouring matter in the same two cells during the progress of the process of concentration. The dark molecules are already for the most part collected about the middle of the body of each cell ; but in the very centre of each cell is a pale point, where the granules seem not yet to have insinuated themselves between the cell-wall and the nucleus. The same capillary is here seen much reduced in calibre.

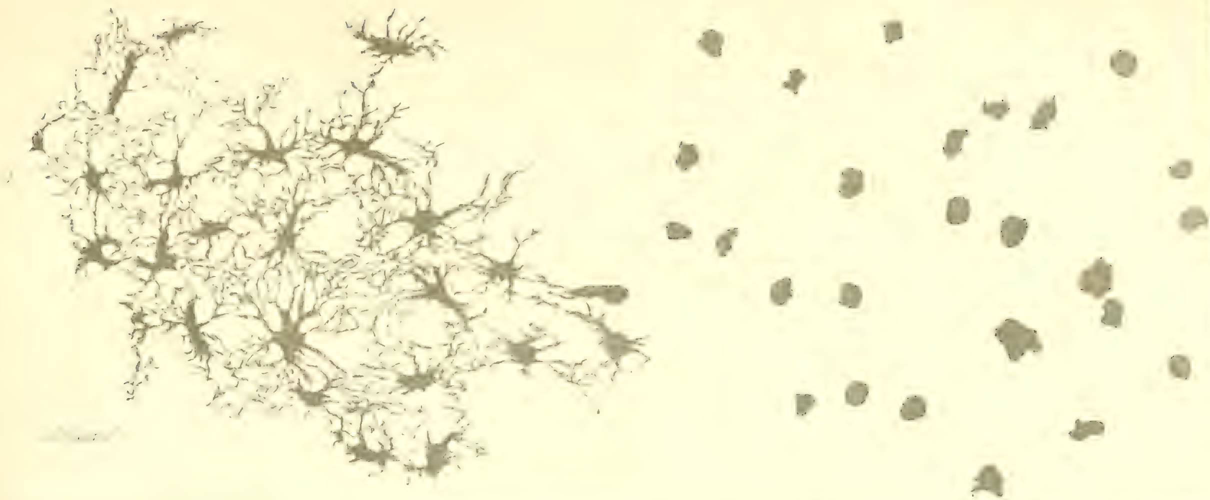
Fig. 5 shows the pigment in the lower of the two cells, concentration being still further advanced.

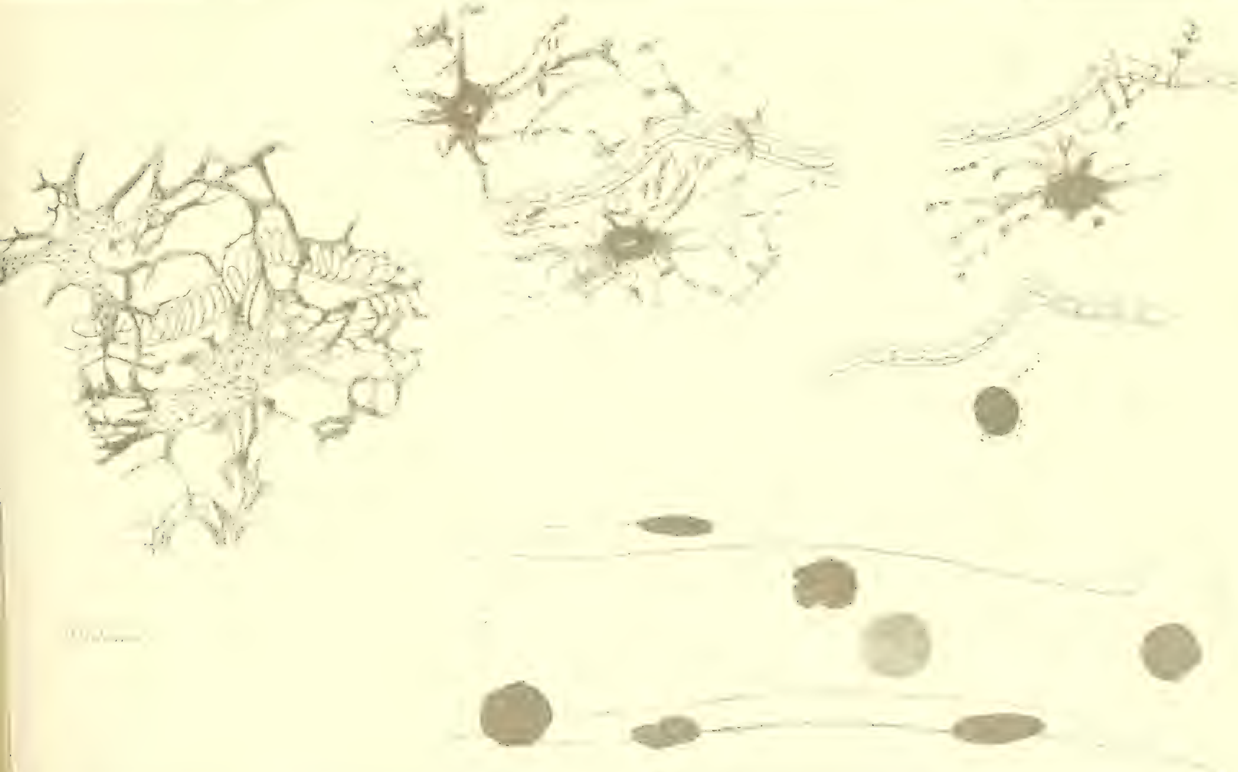
In Fig. 6 the process is seen to be almost absolutely completed, the molecules being almost all of them aggregated into a black circular mass, occupying the middle of the body of the cell, the more circumferential parts of which contain only colourless fluid, and are therefore invisible.

Fig. 7 is an outline of the wall of a large blood-vessel, with chromatophorous cells in its external coat. The pigment is almost completely concentrated, but the form of the section of the black masses, where they are seen edgewise, shows that they are not spherical, but disc-shaped.

Figs. 8, 9, and 10 are drawn, with a much higher power, from young frogs, with small pigment-cells : they exhibit especially the form and relations of the nucleus.

In Fig. 10 the pigment is shown in an unhealthy state, the molecules being irregularly aggregated.





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ON SPONTANEOUS GANGRENE FROM ARTERITIS AND THE CAUSES OF COAGULATION OF THE BLOOD IN DISEASES OF THE BLOOD-VESSELS

Read before the Medico-Chirurgical Society of Edinburgh, March 17, 1858.

[*Edinburgh Medical Journal*, April 1858.]

Mr. President and Gentlemen.—The case which I have the honour to bring before you this evening is one of spontaneous gangrene in a child. The patient was a girl, six years old, who, having had scarlet fever nine months previously, and afterwards suffered severely from dropsy, was seized about the middle of July last with deadly whiteness and coldness of both lower limbs up to a little above the knees. Her mother describes them as having resembled wax in appearance. She and her neighbours rubbed the legs perseveringly, and, after an hour or two, the left limb recovered its warmth and usual aspect, but the other continued in the same state for about two days, when the mother observed some pale blue discoloration between the ankle and the calf. This increased, spreading downwards to the foot ; and, at the same time, undergoing various changes of tint to pink, red, and green, till, at the end of four weeks, the limb presented the appearance depicted in this sketch. [Not here reproduced.] At this time she was brought to the Royal Infirmary, and was admitted into one of the senior surgeon's wards, where, in the temporary absence of Mr. Spence, she came under my care. Her general health appeared remarkably good, considering all that she had gone through : her tongue was clean and moist, and her appetite good, and though her pulse was very quick, viz. 148, this was not to be regarded as a serious symptom in one so young, with such a source of irritation present. Accordingly, three days later, a line of demarcation having distinctly declared itself, I performed amputation immediately above the knee. Very little blood was lost in the operation, which did not accelerate the pulse or impair the appetite even for a day. Three days later, the constitution was evidently experiencing relief from the removal of the disease : the pulse was reduced to 112, and her general aspect improved. The stump healed kindly, and the result was in all respects satisfactory.

The amputated limb having been laid open on its posterior aspect, the gangrene was found to have extended somewhat higher in the deep parts than in the skin; the mortified tissues, including the posterior tibial nerve, were congested in a manner closely simulating inflammation, but of a duller tint, and exactly as far as this congestion extended, the posterior tibial venae comites were turgid, and evidently contained coagulated blood. In the upper part of the limb the veins were flaccid and empty, and all the tissues appeared healthy, except that the popliteal artery, for an inch and a half from its lower end, was the seat of intense congestion, which also implicated slightly the cellular tissue about the vein and nerve. [These appearances were represented in a coloured drawing.] On laying open the vessels, the vein was found pervious and healthy, except that its coats seemed a little thicker than natural, but the artery was filled at the congested part with a coagulum, an inch and a quarter in length, partly pinkish and partly dark in colour. There was no appearance of any inflammatory exudation having taken place into the interior of the vessel, but the clot lay everywhere in contact with the internal coat, to which it was firmly adherent, so much so, as to tear away a portion of it when removed. Beneath the lining membrane were to be seen transverse red streaks, which appeared due to congestion of the circular coat of the vessel. [A sketch of the vessel and its contained clot was now exhibited.] The coagulum extended down the anterior tibial artery as far as to the commencement of the gangrene, but the companion veins were empty and perfectly natural in appearance, as also was the posterior tibial artery.

These pathological appearances clearly indicate that the primary disease was inflammation of the arteries, accompanied by coagulation of the blood within them, obstructing the supply of the nutrient fluid, and so inducing death of the lower part of the limb. This conclusion is in harmony with the previous history, which was from the first that of arterial obstruction.

This case is of practical interest, as illustrating the principle that spontaneous gangrene may be entirely local in its cause, and that in such cases the greatest benefit may be anticipated from removal of the mortified part, provided the constitution be in a state fitted, as regards age and in other respects, for bearing the operation.

But my chief reason for bringing the case now before the Society is because it appears a distinct example of inflammation of the coats of a vessel determining coagulation of the blood within it, without the exudation of lymph into its interior. Not that there is any novelty connected with such an occurrence, but because this effect of arteritis and phlebitis, long recognized by all sound pathologists, appears to be of peculiar interest at the present juncture, in connexion with the recent publication of the last Astley Cooper Prize Essay, in which Dr. Richardson of London propounds the theory, that the coagulation of the blood is due to the escape of a minute quantity of ammonia, which he believes holds the fibrine in solution. I propose, therefore, on the present occasion, to consider how far this new theory accounts for this phenomenon of coagulation in inflammation and other diseases of the blood-vessels.

So short a time having elapsed since the publication of the volume alluded to, it may be well to mention, as briefly as possible, the main facts by which the arguments of the author are supported :- And first I may relate the startling observation made by Dr. Richardson, that if a current of air is passed through two successive portions of freshly drawn blood, contained in two Wolfe's bottles, while that in the first bottle, as might have been expected, has its coagulation accelerated, that in the second bottle is prevented from coagulating for several minutes after the time at which it would have solidified, had it been left in the vessel without interference. In other words, the air has had its properties so modified in passing through the first mass of blood, that it afterwards retards instead of promoting coagulation ; whence Dr. Richardson infers, that it has obtained in its passage some volatile solvent of the fibrine. Secondly, Dr. Richardson has discovered that a very minute quantity of ammonia added to freshly drawn blood keeps it fluid for an indefinite period in a stoppered bottle, but that if exposed to air it coagulates as usual, though at a later period, in proportion to the amount of ammonia employed. He also finds that, by careful management, a fresh clot may be redissolved by means of ammonia, and that after the escape of the ammonia it will again coagulate, and afterwards contract in the usual manner, though more feebly. Next, he finds that ammonia is always to be obtained from the halitus of freshly drawn blood, and although the alkalinity of the blood through soda renders the ammonia excessively prone to escape, so that a good deal is necessarily lost from unavoidable exposure to air, yet he has succeeded in collecting about a third by weight of the smallest amount which he has found sufficient to keep the blood permanently fluid outside the body. Lastly, he has observed that all those circumstances which are known to promote the coagulation of blood outside the body, such as an elevated temperature, free admixture with air, a vacuum, &c., also hasten the process in blood mixed with ammonia, or, in other words, favour the escape of the volatile alkali ; while, on the other hand, those things which check coagulation, such as cold and occlusion from air, prevent or retard the evolution of the gas. To the latter class he has added the remarkable fact that blood remains fluid for many hours under a high mercurial pressure, but coagulates when relieved from it. I confess that, although I was by no means prepossessed in favour of this theory, these facts appear to me to prove irresistibly that the cause of the fluidity of blood, after it has been drawn from the body, is a minute portion of free ammonia holding the fibrine chemically in solution, and that the coagulation of such blood is the result of the escape of the alkali. The only point on which the evidence appeared deficient was the effect of occlusion from air in tubes of dead matter, and this defect I endeavoured to supply by the experiment which I mentioned at the last meeting of the Society, by which I succeeded in keeping the blood of a sheep fluid for three hours within a vulcanized india-rubber tube, the blood coagulating in about two minutes when let out just as if freshly drawn from the veins of the animal.[1] Hence it appears to me that the medical profession is deeply indebted to Dr. Richardson for his laborious and able investigations, which have, as I think, removed much mystery from this long vexed question.

But Dr. Richardson aims at much more than the explanation of coagulation outside the body. He believes that the fluidity of the blood within the healthy living vessels is due simply and solely to the presence of free ammonia, which he supposes to be generated either in the systemic or pulmonary capillaries, and he denies that the walls of the arteries or veins have any effect on the blood by virtue of their vitality, or exercise any other influence upon it than that of checking the evolution of ammonia, just as would be the case were they tubes of dead matter of the same degree of permeability. And all cases of coagulation within the living body are supposed, by him, to be explicable on simple chemical principles. Here, however, I find myself quite unable to follow him. Thus, he believes that the coagulation in an aneurysm is the result of the blood which is at rest in the tumour giving up its ammonia to the current which is flowing past the mouth of the sac. This theory was suggested to him by the following circumstance:—In one of the experiments of transmitting air through successive portions of blood, the longer tube in the last Wolfe's bottle was

[1] This experiment was performed in the following manner:—One of the jugular veins of a sheep having been exposed, it was emptied of blood by passing the finger along it while pressure was applied by an assistant at its anterior part. The vessel was then opened at two places about three inches distant from each other, and into each opening was tied one end of a piece of vulcanized india-rubber tube, a quarter of an inch in diameter, and about eighteen inches long, filled with water, to prevent the introduction of air into the circulation. The pressure was then removed from the upper part of the vein, so as to allow the blood to flow through the tube. It was now easy to ascertain, by observing the collapse of the lower part of the vein, when a part of the tube was momentarily obstructed by pressure, that the circulation was going on freely through the new channel. This having been determined, ligatures of waxed string were tied as tightly as possible round the tube, at intervals of about two inches, beginning at the end next the head and proceeding backwards, so as to avoid all tension upon the enclosed blood, which was, of course, displaced freely in the direction towards the thorax. By this means a number of portions of blood were obtained enclosed in receptacles nearly, though not absolutely, impermeable to gases. The various compartments were opened at different intervals, and up to three hours some of them contained fluid blood which coagulated on exposure, whereas there was in others a considerable portion of coagulum. After four hours, coagulation was almost complete, but a slender thread of fibrine was still obtained from the fluid part in one of the divisions a few minutes after it had been let out.

accidentally too short, so that it did not reach farther down than to about an inch from the bottom of the vessel. The result was, that while the upper part of the blood in this last bottle was retained fluid for a considerable time, that below the level to which the tube reached speedily coagulated. Dr. Richardson infers that the lower portion of blood gave up its ammonia to the air which was bubbling through the upper part sufficiently charged with the alkali to retain that part in a state of fluidity. But, surely, this implies a mistake in chemistry. The lower portion of blood coagulated, I imagine, for the same reasons that it would have done had it been put in a stoppered bottle[1] after passing through the air, though probably not quite so rapidly, while the other part was prevented from coagulating by the ammoniacal vapour bubbling through it.

But if the ammonia theory fails to explain the coagulation that occurs in aneurysm, still more inadequate does it appear to account for the phenomenon in arteritis or phlebitis. How can the fact that the wall of the vessel is inflamed determine, on simply chemical principles, the evolution of ammonia from the blood within it ? Being convinced that in these and other cases of coagulation of the blood in local diseases of the vessels something remained quite unexplained, I have, during the last fortnight, made several experiments, with a view to throwing further light upon the subject, and will now communicate to the Society the results at which I have arrived.

In reflecting upon the matter, some circumstances in physiology and pathology appeared to me to indicate that, on the hypothesis that the blood does contain free ammonia in the living body, the healthy vessels must have a special power of preventing its escape. Thus, the blood in the capillaries of the lungs is separated from the air in the air-cells only by an excessively thin partition of permeable living tissue ; yet Dr. Richardson's experiments have shown that there are times in the day, as, for instance, early morning, in which not a trace of ammonia is given off in the breath. Again, in surgical emphysema, the tissues of the body may be enormously distended with air, without any special tendency to coagulation of the blood in the vessels, such as might be anticipated unless their parietes have a special power of preventing the escape of ammonia. It is true that in this case, the blood being in constant circulation, a perpetual supply of lost ammonia might be maintained from the capillaries ; but it occurred to me that some information might perhaps be gained upon the point in question, by producing emphysema artificially in a limb in which the circulation had been arrested. For this purpose I applied a tourniquet firmly to one of the fore legs of a sheep, just above the elbow, and then injected

[1] This occurrence I have frequently observed.—J. L.

air, by means of a condensing syringe, into the tissues of the lower part of the limb. The struggling of the animal, however, caused repeated displacement of the tourniquet, which I did not succeed in retaining in position for longer than an hour at a time. But, though the experiment was so far a failure, it yielded fruit in an unexpected manner. Having amputated the limb and preserved it, though with little expectation of learning anything from it, I was surprised to find, on examining it six hours later, that, although the cellular tissue about the vessels was still fully distended with air, the blood within them was perfectly fluid, and coagulated in about two and a half minutes, when shed into a saucer. Still greater was my surprise on finding next day, sixteen hours after the amputation, that the blood was still fluid in the vessels ; and though it took longer to coagulate when let out from them, viz. five minutes, did so as fully as before. The muscular irritability, as tested by a powerful galvanic battery, had been found, on the previous evening, to be entirely lost. I next obtained four other feet, with the veins turgid with blood, by applying bandages firmly to the limbs below the joints where the butcher removes them, and amputating above the constricting band, after the sheep had been killed in the usual manner, by the knife. I examined veins in these limbs, day after day, till all the vessels were exhausted, and found at the end of the sixth day after their severance from all connexion with the vascular and nervous centres, that the blood from a deep vein was still perfectly fluid, and coagulated when shed, though the time occupied by the process was now half an hour,—the length of the period having gradually increased, from day to day, since the time of the amputation. The feet, in the meantime, continued perfectly sweet, the coldness of the weather at the time being very favourable for the experiments. Some blood from a subcutaneous vein of the same foot, where decomposition might be expected to occur somewhat earlier, contained, at the same period (the end of the sixth day), some minute portions of coagulum. The fluid part of this blood remained liquid for an hour, but then coagulated well. Hence it was evident that so long as the tissues retained their freshness, the blood within the vessels was kept in a state of fluidity by some agency utterly inexplicable by the ammonia theory. I also found that the same thing occurs in the cat. In one such animal, killed under chloroform, by a knife passed into the great vessels of the neck, the blood in the veins of the extremities remained perfectly fluid after forty-eight hours, and coagulated when shed. In another cat, killed by asphyxia, the same was the case as regards the posterior extremities ; but the veins of the fore legs contained particles of coagulum, like the subcutaneous vessel of the sheep's foot. This difference I am inclined to attribute to the fact that the animal made violent and protracted exertion with the fore legs during the death struggle, thus exhausting their vital energies more than those of the other limbs. After four days, however, the blood in the hind legs, though still fluid, with the exception of very minute particles of coagulum, had lost its power of coagulation. This increasing slowness and final absence of coagulation in blood long kept within the vessels is curious, and must, I imagine, depend upon some gradual change in the properties of the fibrine.

We have seen that in two classes of the higher animals, differing from one another as widely as the carnivora and herbivora, and after modes of death so various as haemorrhage, asphyxia, and an operation performed under chloroform, the blood remains fluid in the vessels, though perfectly at rest, for days after death. It may appear almost incredible that a fact of such fundamental importance, and at the same time so easy of demonstration, should have escaped the observation of all the eminent men who have made the coagulation of the blood a subject of special study; yet such appears to be the case. Dr. Richardson speaks of occasional instances of fluidity of the blood after death, and coagulation on exposure, but considers it quite essential for such an occurrence that the vascular system should not have been opened by wound, though it is difficult to see how such a circumstance could affect the question, according to his theory, except on the supposition that the blood-vessels were impermeable to gases in solution. Again, Dr. Davey, in his *Researches*, writes as follows :—' The blood, after death, I have often found liquid, and that many hours after death, when cold, but still retaining its power of coagulating'; but he had no idea of fluidity and coagulability lasting for days after death, or even for hours, except in rare instances. The nearest approach which I have been able to find to such an observation is contained in that inexhaustible treasury of original observation and profound reflection, the works of John Hunter, where the following passages occur :—' As a proof that blood will not coagulate in living vessels, in a perfect and natural state, and ready to act when powers were restored to it, I found that the blood of a fish, which had the actions of life stopped for three days, and was supposed to be dead, did not coagulate in the vessels, but, upon being exposed or extravasated, soon coagulated. . . . The blood of a lamprey-eel, which had been dead to appearance some days, was found fluid in the vessels, because the animal was not really dead: there had, however, been no motion in the blood, as the heart had ceased acting; but upon its being exposed, or extravasated into water, it soon coagulated' (Palmer's edition, vol. iii, p. 32). Hunter, however, does not seem to have drawn any inference with regard to the higher animals from these cases. He speaks of ' the very speedy coagulation of the blood which usually takes place in all the vessels after death' (vol. iii, p. 27); and though he believed that 'where there is a full power of life, the vessels are capable of keeping the blood in a fluid state', he also supposed that some motion, though 'very little, is required to keep up its fluidity' (ib., p. 32). Indeed, the expression, 'full power of life,' just quoted, is quite inconsistent with the state of a sheep's foot, six days after muscular irritability has been lost. I had myself frequently made experiments on inflammation upon the amputated limbs of frogs, and observed that the blood remains fluid for more than twenty-four hours after death; but muscular irritability, ciliary action, &c., also last in those creatures to a very much later period than in the higher animals, so that I never ventured to infer that fluidity of the blood was likely to continue long after death in mammalia.

Further observations on the feet of the sheep and limbs of the cat proved even still more strikingly the influence of the vessels upon their contained blood. If the skin be reflected from over a subcutaneous vein full of blood, and lightly replaced, so as to protect the subjacent parts from evaporation, without excluding the air, the vessel will be found, in two or three hours, changed from a dark venous colour to a scarlet arterial tint; yet no coagulation will occur in the blood, although the oxygen of the atmosphere has evidently penetrated freely through the coats of the vessel, showing that abundant opportunity has occurred for evolution of ammonia, provided any tendency to such an occurrence existed. Again, if such a vein be cut across with fine sharp scissors, without disturbing its connexions, or inflicting much injury on its coats, the blood will be found, after about six hours, perfectly fluid in the vein, up to within perhaps 1-20th of an inch of the wound, where a small clot is perhaps seen, utterly insufficient to obstruct the progress of ammoniacal vapour. Hence it appears to me to follow, as a matter of demonstration, that, if free ammonia really exists in the blood within the vessels, the circumstance of its being in those vessels deprives it entirely of its volatility; and that, whether the ammonia be free in the blood or not, its chemical tendencies, such as it exhibits outside the body, are in some manner entirely modified by the vicinity of the vascular tissue. With regard to the nature of the modifying influence, no other explanation appeared to offer itself than that it depended upon residual vitality in the tissues.

In order to prosecute the investigation of the cause of coagulation in arteritis or phlebitis, I endeavoured to produce artificially, as nearly as practicable, in a living animal, the condition in which the vessels are when inflamed. Having proved, as I think I may venture to say—by investigations, an account of which will shortly appear in the *Philosophical Transactions*[1]—that inflammation consists in an impairment of the vital energies of the tissues of the part

[1] See p. 209 of this volume.

affected, I resolved to destroy the vitality of a vein, and then permit the blood to flow through it for some time, and ascertain whether coagulation would occur in spite of the current, as it must do in phlebitis.[1] The agent which seemed best adapted for inflicting the lesion was strongest liquor ammoniae, both on account of its rapid action, and also from the circumstance that, as Dr. Richardson has shown, its chemical effect upon the blood, whether applied concentrated or diluted, is to prevent coagulation. On the 8th inst., having exposed one of the jugular veins of a sheep, and isolated it from surrounding connexions for six inches of its length, carefully avoiding even momentary obstruction of the flow through it, I placed a plate of glass beneath the vein, to protect the neighbouring tissues from the action of the alkali, and at $3^{h}\ 13^{m}$ p.m. emptied the portion of vein of its blood, by stroking the finger along it, while an assistant exerted gentle pressure on the anterior part, and then at once applied the liquor ammoniae thoroughly, with a camel's hair brush, to all sides of the vessel throughout the length exposed. The application of ammonia occupied three-quarters of a minute, and three-quarters of a minute later the blood was again allowed to flow through the vessel, having been arrested altogether a minute and three-quarters. A short time having been allowed for the evaporation of the ammonia, the edges of the wound were brought together with stitches. At $4^{h}\ 58^{m}$, or an hour and three-quarters later, the wound having been opened, the flow was again obstructed as before, and the vein was rapidly slit up. A small amount of dark coagulum escaped with the fluid blood. The interior of the vessel was now immediately examined. A valve with three flaps, about the middle of the opened portion, was rendered conspicuous from the fact that a black coagulum existed between each of the flaps and the wall of the vessel ; and on careful observation of the lining membrane of the vein in other parts, it was seen to be dotted over in patches with fine granular deposits of pink fibrine, which could only be detached by firmly scraping with the edge of the knife, reminding me precisely of the close adhesion of the clot which occurred in the popliteal artery in the case which I related at the commencement of this paper, and which is known to be characteristic both of arteritis and phlebitis. Here it is clear that the coats of the vessel having been deprived of their vitality, the blood flowing through it assumed

[1] Sir Astley Cooper performed experiments to show the effect of mechanical injury of the coats of a vein upon the coagulation of the blood at rest within a portion of the vessel contained between two ligatures ; and he came to the general conclusion, that loss of vitality in the vessel greatly accelerated the process of coagulation. Dr. Richardson alludes to these experiments, but says they have been invalidated by subsequent investigations by Scudamore. I have not as yet seen Sir Astley's own account of his researches on the subject, but, from a notice of them by Palmer, in his edition of Hunter's works, I suspect that they do not deserve to be set aside so lightly.

the same chemical tendencies as we have seen it to possess when removed from the body; and those parts of the fluid which remained at rest under these conditions, namely, the motionless layer of liquor sanguinis next to the lining membrane, and the portions of blood in the sinuses of the valve, underwent coagulation, yielding up their ammonia through the permeable coats of the vein. And I think we need not hesitate to admit that similar occurrences take place in the early stages of arteritis and phlebitis, the coats of the vessels being in those cases not dead, but impaired in vital energy by inflammation.

A similar explanation appears to account for the early formation of coagula in the vicinity of a ligature placed upon an artery. It has been seen how utterly the usual explanation, that of the quiescence of the blood, fails to account for the phenomenon; but the fact that lymph is afterwards exuded from this part of the vessel shows that the case is really one of limited traumatic arteritis.

But if the coagulation within inflamed vessels thus receives a solution from the results of the last-mentioned experiment, still more unequivocally, at least to most of my hearers, is the coagulation in gangrene explained, such as occurred, for instance, in the case which has been described.

Again, it is well known that contused wounds bleed very little, the ends of the divided arteries becoming speedily plugged with a long coagulum. The only explanation which Sir Charles Bell could offer of this remarkable provision of nature was, that the living vessels had a special faculty of preventing the blood from exercising friction upon their lining membrane, but that the contused artery, having lost its vitality, the blood became arrested by friction and coagulated. We now see that there was much more truth in this theory than has been generally supposed, though the loss of vitality in the vessel does not operate in the manner which Sir Charles imagined.[1]

It has been found difficult to understand why the fact of the arteries being converted into calcareous tubes should impress upon the blood within them a tendency to coagulate in atheromatous degeneration of the vessels. The impairment, or entire loss of vitality connected with such a condition, will now be found a sufficient explanation.

The coagulation in aneurysm is now equally comprehensible, the walls of the sac consisting either of degenerated or torn coats of the vessel, of inflamed surrounding tissues, or of layers of fibrine, each of these constituents being in a state of very low vitality.

The rapid coagulation of lymph, which appears to be neither more nor less

[1] I find I have not done justice to Sir C. Bell's views upon this subject. In his later works he expresses the opinion that the lining membrane of the living vessels possesses the power of 'preserving the blood fluid', and that the cause of coagulation in a contused artery is the loss of this power in consequence of the injury.—Vide Sir C. Bell's *Institutes of Surgery*, vol. i, p. 52, and vol. ii, p. 277.

than the fibrine of effused liquor sanguinis, contrasts, in a very striking manner, with the lengthened period during which blood extravasated into the cellular tissue may retain its fluidity. But the fact that the liquor sanguinis is exuded among tissues that are in a state of inflammation, and so impaired in their vital energies, renders the circumstance in question easily intelligible.

With regard to the nature of the influence exercised by the living vessels upon the blood within them, it might be conceived to be either of a positive or negative character. It might be imagined, either that the blood has a natural tendency within the vessels to comport itself as it does when outside the body, and that this tendency is counteracted by an active operation of the living tissues, or, that the vital fluid tends to no such change except when prejudicially acted on by surrounding objects, which in that case might be supposed to exert upon it attractive forces such as tend to group the molecules of dead matter together in aggregation, while the living tissues were destitute of such action, and simply neutral in their conduct towards the blood. Of these, the former has always appeared to me the more likely, *a priori*, but I had not expected to have met with any facts to give distinct evidence either in one direction or the other upon a subject so recondite. A simple observation, however, made on the sheep's foot, appears to throw clear light on the matter. I have frequently observed that when a vein has been opened and has remained patent, the blood has continued fluid in the aperture for a very much longer time than is necessary to produce coagulation of a portion of that blood placed in a saucer. When the wound in the vein has been a narrow one, I have seen the blood remain fluid between its lips for three hours together, though perfectly at rest. I have even observed where a portion of fluid blood has been pressed from a vein into a groove in the tissues, formed by muscle below, periosteum on one side and tendon on the other, this portion of blood has remained fluid for an hour, while another drop removed into a saucer at the same time from the same vein, has coagulated in a quarter of an hour. Now, in all these cases the blood was fully exposed to the influence of the atmosphere ; and if the air had been an active agent, promoting the tendency to coagulate, and the tissues merely neutral in their operation, coagulation must have occurred rapidly. On the other hand, if we admit that the tissues exert an active influence on the blood, and that air, oil, and other inorganic matter is inert with regard to it, the retarded coagulation follows naturally.[1] Here, then, it appears to me, we

[1] Since this paper was read, I have obtained further evidence which will, I trust, appear quite conclusive regarding the entirely negative influence of the atmosphere upon the blood, with respect to promoting the tendency to coagulation. Just forty-eight hours after the death of the sheep which furnished preparations exhibited to the Society, I exposed a vein of one of the feet and injected air forcibly into it, by means of a condensing syringe with a fine injection pipe adapted to it. Seven hours

have a sure, though imperfect glimpse, of the operation of mysterious but potent forces, peculiar to the tissues of living beings, and capable of reversing the natural order of chemical affinities ; forces which I suspect will never be fully comprehended by man in the present state of his existence, and the study of which should always be approached with humility and reverence.

Having thus obtained evidence of the active operation of the living tissues upon the blood, it occurred to me that the walls of the vessels might probably act to greater advantage upon their contents when of small than of large calibre, and that, in that case, the blood might be found fluid in the small vessels of the human body after death, although coagulated in the heart and large vessels. Accordingly, I have examined three human bodies with regard to this point, and in every case have found my idea confirmed. One of these was a woman, aged seventy, who had been a patient under Dr. Gillespie's care at the Infirmary, with senile gangrene. The right cavities of the heart were full of blood, and contained large clots buffed on their upper surface, and the large vessels also contained abundant soft coagula, but a small vein from one of the thighs yielded fluid blood, which coagulated slowly in a saucer. The body was examined about thirty-six hours after death. The other two had been patients under Dr. Gairdner's care, also in the Royal Infirmary. One of these was a man about thirty, who had died of meningitis. The heart had been removed before I saw the body, but the large vessels, such as the external iliac vein, contained coagula, whereas all the small veins which I observed contained perfectly fluid blood, which, however, had lost the power of coagulation. The third case was that of a young man, aged twenty-one, who died of a complication of medical and surgical complaints, nearly forty-eight hours before the body was examined. The corneae were perfectly clear, and there was no appearance of any incipient decomposition. This case was investigated very carefully ; and as the subject is novel, it may be well to give the results in detail :—I was not present

later I again examined the foot, and on reflecting the skin from the opposite aspect of the limb, found there a large subcutaneous vein distended with a mixture of blood and air ; the latter, which had evidently passed through an anastomosing channel, being present in the form of very numerous large and small bubbles. Having secured the ends of a long piece of this vein, I dissected it out and shed its blood into a saucer. Not a particle of clot existed in the vein, and complete coagulation took place within a quarter of an hour. The vein which had been exposed, in order to inject the air, contained here and there portions of clot in the exposed part, the vitality of the vessel having doubtless been impaired by the mechanical violence to which it was subjected in the dissection, or by the drying influence of the atmosphere.

In order to illustrate the effect of mechanical violence applied to a vessel in promoting the coagulation of the blood within it, I pinched a vein of the same foot severely with dissecting forceps in about an inch of its length, at the same time that I injected the air into the other vein. On examining the foot, seven hours later, the vein which had been pinched contained coagulum in the part which had been so treated, but fluid blood in the rest of its extent, both above and below the injured portion.—J. L., March 19, 1858.

when the heart was removed, but Dr. De Fabeck (resident physician under Dr. Gairdner) informs me that the cavities contained coagula buffed on their upper surface. The vena cava, the right iliac veins (common, internal, and external), and the femoral vein for about four inches down the thigh, contained soft coagula, mixed with thick dark fluid blood. The upper part of the axillary vein and the internal jugular of the same side, also contained some soft dark coagula, but the deep epigastric, the femoral vein below the part before mentioned, the internal saphena, and a smaller venous branch in the thigh, the axillary, except at the upper part, the cephalic, and a subcutaneous vein of the throat, all contained fluid blood, which coagulated in about half an hour after being shed ; and I noticed in the thigh that the blood from a small venous branch coagulated more quickly than that from the saphena. In the veins of the lower limb, both large and small, there were curious strings of highly elastic tawny fibrine, but these had evidently been deposited long before death. Similar threads were also present in the veins of the neck and in the aorta, external iliac, and femoral arteries, which, however, contained but little blood, and no post mortem coagula. I did not test the coagulability of the blood in the arteries, nor in a branch of the internal iliac vein, which also contained fluid blood.

I am aware of one source of fallacy in these experiments, namely, that the abdominal viscera are subject to decomposition before the limbs ; and as soon as decomposition does set in, the blood coagulates in the parts which are the seat of it ; as, for example, in small veins of the intestines. This cause of error was, however, I think, guarded against in the last case ;[1] and considering the

[1] Through the kindness of my friend Mr. John Gamgee, of the New Veterinary College, I have had the opportunity of making further observations regarding this point, upon an animal with very large blood-vessels, so soon after death as to avoid the risk of incipient decomposition. A healthy horse having been killed by pithing, at 11.30 p.m. on the 22nd inst. (March 1858), I examined the body just twelve hours later, while it was still warm. The cavity of the thorax, when opened, smelt perfectly fresh. Both auricles contained large masses of coagulum, buffed on their upper surface. There were also soft dark clots in both ventricles, together with a good deal of fluid blood, which, however, scarcely coagulated at all, a considerable portion from the right ventricle yielding, after many minutes, only a minute thread of fibrine. I suspect this was chiefly serum and corpuscles, which had passed in from the auricles on relaxation of the ventricles. There was a considerable amount of firm coagulum in the aorta, and the large veins at the anterior part of the chest were loaded with firm buffed clot. A small branch beneath the pleura, where it is reflected over the pericardium, contained perfectly fluid blood, as also did a coronary vein of the heart, about as large as the saphena of the human thigh ; whereas the concomitant artery, which was very large (bigger than the human femoral), had the blood a good deal coagulated. That from the coronary vein, having been shed into a saucer, yielded, after some time, threads and lumps of fibrine. An intercostal vein, from beneath the pleura, as big as a crow-quill, furnished fluid blood, which coagulated. The superficial veins of both fore-legs yielded perfectly liquid blood, which began to coagulate in about four minutes, and set into a solid mass. But, just below the axillary, small portions of coagulum made their appearance in the vessels, which here attained a size about equal to the femoral in man ; and both the axillary trunks were plugged with firm clot.

almost universal occurrence of coagulum in the heart of the human subject twenty-four hours after death, compared with the universal absence of it in the small veins of healthy parts, so far as I have yet examined them, both in man and the lower animals, I think the fact must be admitted, that where a large mass of blood exists within a cavity of the heart or a blood-vessel, it experiences coagulation sooner than if in a small vessel of the same body. If this be admitted, it becomes a strong argument in favour of the active operation of the tissues, for the blood is more exposed to the influence of the air in a subcutaneous vein than in the heart, and the only conceivable reason for the greater persistence of fluidity in the latter than in the former is that the influence of the tissues operates to greater advantage upon the smaller mass of blood.

Again, supposing it to be admitted that free ammonia exists within the blood-vessels, maintaining the fibrine in solution, a hypothesis which, I confess, appears to me very probable,—granting the ammonia theory, I say, as far as it can possibly be granted, it is clear that no merely neutral action of the tissues could check the evolution of the alkali in the manner above described ; and nothing can tend to convince us more of the potency of the vital forces than to consider what new powers must be impressed upon the chemically inert constituents of the tissues, in order to enable them securely to chain down the alkaline gas, in spite of its excessive volatility.

There is one other experiment upon the sheep's foot which I do not like to omit mentioning. Having exposed a subcutaneous vein, six hours after the death of the animal, I pressed out the blood from an inch of it, and treated the empty part with caustic ammonia, the adjacent parts being protected by olive oil. When the smell of ammonia had passed off, I let the blood return, and, two or three hours after, found that the portion which had had its vitality destroyed by the ammonia, was full of clot, while the blood in the adjacent parts of the vein was fluid, and coagulated on exposure.[1]

This, however, was not the only result of the application of the ammonia. The surrounding tissues had not been thoroughly protected from its action by the oil, and next morning all the parts on which it had acted were the seat of the most intense congestion, accompanied with exudation of glairy matter into the cellular tissue ; in fact, there were all the appearances of the most severe

[1] Two feet of a sheep, killed six hours before the Society met, were exhibited in illustration. One of these was prepared in the manner described in the text. The portion of vein which had been treated with ammonia contained a cylindrical coagulum, while the blood in the adjacent parts of the same vessel was fluid. The other foot was for the purpose of showing the fluidity of the blood so many hours after death. A considerable amount having been shed into a saucer in the liquid state, soon assumed the solid form.

inflammation. Some of the exuded matter had trickled down on a board beneath, and had there coagulated, showing that genuine exudation of lymph had been the result of this post mortem inflammation, then, I believe, for the first time observed in one of the mammalia.[1] I cannot avoid expressing the satisfaction that it has given me to find what I had inferred from other circumstances, in my investigations on inflammation, now established as a matter of observation. I had found that the blood-corpuscles, both red and white, were perfectly free from adhesiveness within the vessels of a healthy part, but that in an inflamed region they stuck together just as they are seen to do between two plates of glass. Having thus observed that the corpuscles of the blood comport themselves in an inflamed part in the same manner as in blood drawn from the body, I inferred that the liquor sanguinis was, in all probability, similarly affected, although coagulation is not observed in the capillaries, in consequence of the movement of the blood; and I gave the same explanation of the speedy coagulation of lymph, and of the formation of clots in inflamed vessels, as has been substantiated by independent facts this evening. In the paper before alluded to, the following passage occurs :—'The non-adhesiveness of the red and white corpuscles, and the fluidity of the blood, seem to be due to one and the same mysterious and wonderful agency—the tissues of a healthy body appearing to extend over the blood near them, a part of the same influence by which they are themselves protected from the action of chemical affinities tending to their decomposition.' We now see that when an agent capable of producing inflammation acts upon a part in which the blood is at rest, coagulation of the blood does really occur in the vessels.

There is an error of observation into which Dr. Richardson has unaccountably fallen, which it appears important to correct. In speaking of the coagulation of a portion of blood enclosed between two ligatures in the jugular vein of a dog or cat, he mentions the formation of a large bubble of air within the vessel, a little prior to the occurrence of coagulation. I have frequently seen the pellucid appearance he describes, but find that it is in no way connected with coagulation, but is due to the subsidence of the red corpuscles, leaving a layer of clear liquor sanguinis at the top. If two ligatures be applied, about an inch apart, upon a subcutaneous vein of one of the legs of a cat, care having been taken not to disturb the connexions of the vessel, or inflict injury upon it, and the leg be suspended by the paw in the vertical position, the clear appearance will begin to show itself below the upper ligature within five minutes.

[1] Tension upon the blood in the vessels, resulting from the bandage, supplied, I imagine, the place of the force of the heart in squeezing out the liquor sanguinis through the walls of the capillaries, deprived of their usual power of retaining it.

If now the limb be left for several hours, the skin having been carefully replaced so as to prevent evaporation, the clear colourless upper layer will be found to occupy nearly two-thirds of the length of the portion of vein, and to be sharply defined from the black lower layer which contains all the red corpuscles. If now the upper part be punctured, the clear liquor sanguinis will flow out, and coagulate upon any object held to receive it.[1]

Some of the observations above described will have a bearing upon medico-legal inquiries, showing, as they do, that not only ecchymosis, which some have denied, but even inflammation may be developed post mortem, provided that the return of blood by the veins is in some way prevented.

There are other bearings, both upon pathology and practice, to which I cannot even allude on the present occasion ; but I thought it best to place the facts at once before my professional brethren, confident that they will receive from them all the attention that they may deserve.

In conclusion, I have to express my thanks to my friend, Mr. Craig, for the kind and able assistance which he has afforded me throughout this investigation, and also to my friends, Drs. Gourlay and Hill, who have on several occasions lent me most valuable aid.

[1] Post mortem congestions simulating inflammation are, I suspect, due to this gravitation of the red corpuscles of the still fluid blood into the vessels of dependent parts.

A CASE OF LIGATURE OF THE BRACHIAL ARTERY, ILLUSTRATING THE PERSISTENT VITALITY OF THE TISSUES

[*Edinburgh Medical Journal*, vol. iv, p. 119, August 1858.]

On the 28th of May last I was requested to see a case at Balfron, in Stirlingshire, under the care of Mr. Burgess, who stated that on the 10th of April the patient, a man about fifty years of age, inflicted a suicidal wound with a razor on the front of the left arm about three inches above the elbow, severing the biceps completely and dividing both the main superficial veins of the limb. The bleeding was very profuse but chiefly venous, and was readily controlled by pressure, and the wound was afterwards lightly dressed without anything unusual occurring for several days, when haemorrhage again took place to a very alarming extent. It was treated as before by compression, but recurred twice at intervals of a few days, after which for a period of more than three weeks the healing process appeared advancing favourably. On the 24th of May, however, there was another discharge of blood from the wound, and this was repeated at frequent intervals and with increasing violence in spite of compression, until the 27th, when it became imperative to have recourse to other measures. Inconvenience in the arrangements of the railway delayed my arrival nearly a day, and in the meantime it had been found necessary to apply bandages at the seat of wound with all possible force, so as completely to arrest the flow of blood through the vessels of the limb, which had thus been entirely devoid of circulation for about thirty hours before the time at which I first saw the patient, viz. 2 p.m. on the 29th. At this time he was lying in bed pale and weak from loss of blood with the left arm somewhat swelled below the bandages, livid in tint and quite cold. Chloroform having been administered I removed the bandages, after which arterial blood gushed from the wound as soon as the pressure of the fingers over the brachial artery was relaxed. With the assistance of Mr. Burgess I proceeded to expose the bleeding-point, and after a somewhat troublesome dissection among the tissues, densely matted together with inflammatory deposit, discovered a small wound in the brachial artery, and having cleared the vessel sufficiently to avoid the risk of including either of the adjacent nerves, passed ligatures around it above and below the aperture, with the effect of removing all tendency to haemorrhage. Before I left in the afternoon the limb had already recovered its warmth and Mr. Burgess has since informed me that feeble pulsation was soon after perceptible at the wrist. In his last letter, written on the 21st of June, he stated that the ligatures had come away several days previously, the wound was healing kindly, and there was good sensation in the limb, though not quite so acute as in the other arm, while the patient was regaining health and strength.

This case is an example of the practical application of the principles sought to be established in a paper lately published in this journal,[1] in which it was shown that tissues previously healthy retain their vitality for a much longer period than had been before supposed after complete withdrawal from the influence of the centres of circulation and innervation; and that by virtue of this persistent vitality the blood continues fluid for several days within the vessels of an amputated limb. In the present case the appearances of the arm and the previous history were such as would, I believe, have induced most surgeons not conversant with these principles to have resorted at once to amputation.

[1] Vide a paper by the author 'On Spontaneous Gangrene from Arteritis and the Causes of Coagulation of the Blood in Diseases of the Blood-vessels'. *Edinburgh Medical Journal*, April 1858 (p. 69 of this volume).

PRELIMINARY ACCOUNT OF AN INQUIRY INTO THE FUNCTIONS OF THE VISCERAL NERVES, WITH SPECIAL REFERENCE TO THE SO-CALLED 'INHIBITORY SYSTEM'

In a Letter to Dr. Sharpey, Sec. R.S.

[*Proceedings of the Royal Society of London*, vol. ix, No. 32 (1858).]

Received August 13, 1858.

My dear Sir.—The fact that the irritation of visceral nerves sometimes causes arrest of the movements of organs supplied by them, as shown by Edward Weber's experiment of stopping the action of the heart by stimulating the vagus, and by Pflüger's more recent observation that the application of galvanism to the splanchnic nerves produces quiescence of the small intestines, appears to me to have an intimate bearing upon the question how inflammation is developed through the medium of the nervous system at a distance from an irritated part; and as the nature of the inflammatory process has lately engaged my special attention, I have been led to make an experimental inquiry into this 'inhibiting' agency, the true interpretation of which is, as you are aware, still *sub judice*. I now propose to state the principal results at which I have arrived, reserving further details for a more extended communication which I hope soon to offer the Royal Society.

The view which has been advocated by Pflüger,[1] and I believe very generally accepted, viz. that there is a certain set of nerve-fibres, the so-called 'inhibitory system of nerves' (Hemmungs-Nervensystem), whose sole function is to arrest or diminish action, seemed to me from the first a very startling innovation in physiology; and you may possibly recollect my mentioning to you in conversation, when in London last Christmas, my suspicion that the phenomena in question were merely the effect of excessive action in nerves possessed of the functions usually attributed to them. On further reflection upon the subject, the consideration of the contraction produced in the arteries of the frog's foot by a very mild stimulus, as compared with the relaxation of the vessels caused by stronger irritants acting through the same nerves, confirmed my previous notions. For I could hardly doubt that the cause of the

[1] Eduard Pflüger, *Ueber das Hemmungs-Nervensystem*, 1857.

quiescence of the heart or intestines on irritation of the vagus or splanchnic nerves was analogous to that of arterial dilatation in the web, and that, provided a sufficiently mild stimulus were applied to the so-called 'inhibitory nerves', increased action of the viscera would occur, corresponding to the vascular constriction.

To test the truth of this hypothesis, I made several experiments between the 17th of June and the 14th of July of this year, with regard to the movements of the heart and intestines. The means used for stimulating the nerves and spinal cord were sometimes mechanical irritation, but more commonly galvanism, applied with a magnetic coil battery of a single pair of plates, the strength of which could be regulated in a rough way, with great facility, by the height at which the acid solution stood in the jar and the extent to which the rods of soft iron were inserted in the helix. The mildest action employed was such as was but just perceptible to the tip of the tongue, placed between the fine silver-wire extremities of the poles, when the rods were fully in the helix, but inappreciable after their complete withdrawal; the spring carrying the magnetic bar being made to vibrate by a touch with the finger: the greatest action of the battery, on the other hand, was so powerful as to elicit sparks when the poles were applied to the tissues.

My attention was first directed to the intestines, and it may be well to mention first all the results obtained with reference to them. The animals operated on were generally rabbits, they being very easily managed, and also favourable for the purpose on account of the large amount of movement which occurs in their intestines. Chloroform was generally not administered, on account of its depressing effect upon the action of the nervous centres.

In the first experiment, the ends of the poles having been fixed to the spinous processes of the ninth and twelfth dorsal vertebrae, according to Pflüger's original method, and the intestines allowed to protrude through a wound in the abdominal parietes, a series of interrupted currents were transmitted, a very small amount of acid being in the jar, and the rods fully in the helix. The effect was complete relaxation and quiescence of the small intestines, which had been previously in considerable movement, while the muscles of the limbs were thrown into spasmodic action; but on the discontinuance of the galvanism the previous intestinal motion returned. The rods were then removed from the helix, and the battery, thus diminished, was applied on several occasions, with markedly increased action of the intestines in every instance during the first twenty-five minutes. In the next half-hour the increase of action from the galvanism, though still distinct, was less strongly marked; and at the end of that period, the rods having been reintroduced, the inhibiting influence was also found to be much less complete than before, indicating that the parts of the nervous apparatus concerned were in a less active condition, no doubt in consequence of exhaustion. The arches of the tenth and eleventh dorsal vertebrae having been removed before the experiments with galvanism, I subsequently introduced a fine needle into the exposed part of the cord, with the effect of causing in repeated instances increased movements of the intestines, which were especially striking on account of the occurrence of peculiar local contractions not seen at other times. Further observations upon this animal tended to confirm those which have been mentioned, as did an experiment of the same kind performed the next day upon another rabbit.

I afterwards found that the best mode of proceeding was to remove the skin and one or two layers of muscles from a portion of the abdomen till the parietes were sufficiently thinned to permit the intestines to be distinctly seen through them ; by this means the complication produced by exposure of the intestines to the atmosphere was avoided, and the most satisfactory results were obtained ; the increase of the peristaltic movements during the transmission of extremely feeble shocks being strikingly apparent and constant on every occasion. During the experiment performed in this way I noticed several times that a violent struggle on the part of the rabbit, when the intestines were in pretty free movement, was followed by absolute and universal quiescence of those organs for several seconds ; this appeared to me of great interest, as proving that the inhibitory influence is certainly sometimes exerted in the natural actions of the animal, and is not merely the result of artificial stimulation.

In the course of the above experiments several other observations were made. In the first place I verified the statement of Pflüger, that if, when the intestine is lying relaxed under the inhibiting influence of galvanism applied to the spine, a particular part be irritated, local contraction occurs, but is not propagated to neighbouring parts. This fact is of fundamental importance, since it proves that the inhibitory influence does not operate directly upon the muscular tissue, but upon the nervous apparatus by which its contractions are, under ordinary circumstances, elicited.

Another point which seemed to require investigation was the well-known increase of peristaltic action which takes place after death, and which continues in spite of cutting off the mesentery close to the gut. Those who believe in a constantly restraining function of certain nerves during life might argue that the intestine has always a tendency to such active movements, but is kept in check by the ‘ inhibitory nerves ’, and released from their control when they have lost their power after death. A different explanation, first suggested, I believe, by Bernard, is that the increased action of the intestines is the result of failure of the circulation in the part ; and to this view I felt disposed to agree.

in consequence of having noticed curious irregular contractions in the arteries of the frog's foot from a similar cause. In order to decide the question, I tied three adjoining arterial branches in the mesentery of a rabbit, thus depriving about three inches of the intestine of its circulation, the parts so affected being accurately defined by the extent of absence of pulsation in the minute vessels close to the gut. In about a minute and a half, vermicular movements commenced in this part, the rest of the intestines being at the time very quiet. Powerful interrupted galvanic currents were then transmitted through the posterior dorsal region of the spine, with the effect of causing perfect quiescence of the whole of the intestine, including the part whose arteries had been tied. After cessation of the galvanism the movements recurred in the portion devoid of circulation, while elsewhere they were almost entirely absent. This experiment was repeated on another occasion with similar results. In one of the cases I divided the mesentery close to the gut, after ligature of the vessels, but no change took place in the character of the movements which had been previously induced, indicating that the increased action in these cases had been of the same nature as that which results from death. The arrest of the movement on the application of galvanism proved that the delicate operation of ligature of the mesenteric vessels had been performed without injury to the adjacent nervous branches; and it therefore followed that the movement in the parts supplied by those vessels was not due to any injury of the nerves, but simply to the arrest of circulation. It further appears from these experiments, that, in whatever way the cessation of the flow of blood through the vessels operates in increasing the peristaltic action, it does so through the medium of the nervous apparatus, and not by directly influencing the muscular tissue. For, in the latter case, the movement would have continued in spite of the inhibiting influence, which, as we have seen, has no effect upon muscular irritability.

The fact that the movements continue in a portion of gut deprived of its mesentery, proves that the nervous apparatus by which the muscular contractions are induced and co-ordinated in post mortem peristaltic action, is contained within the intestine.

The distinction between the co-ordinating power and muscular contractility was very strikingly shown in the further progress of one of these experiments. The peristaltic movements of the portion of gut supplied by the ligatured arteries ceased entirely about twenty minutes after the vessels were tied, and the surface of the gut became there perfectly smooth and relaxed, contrasting strongly with the wrinkled aspect of other parts. But muscular irritability had outlived the co-ordinating power, as was shown by energetic, purely local contraction taking place in a part pinched. Similar observations confirmatory of this point were afterwards made upon a rabbit which had died of haemorrhage an hour before.

The mechanism by which the muscular contractions are regulated is, doubtless, the rich ganglionic structure lately demonstrated in the submucous tissue by Dr. Meissner of Bâle.[1] Professor Goodsir gave me the first information of the anatomical fact on my mentioning to him the foregoing physiological proofs of the existence within the intestines of a co-ordinating apparatus distinct from the muscular tissue. I have since verified Meissner's observations, and found abundant well-marked nerve-cells in the submucous tissue of the ox, exactly corresponding with his descriptions.

But while muscular irritability outlives the co-ordinating power in the intestines, the latter lasts much longer than the inhibiting property in the spinal system, for I find that Pflüger's experiment does not succeed in a dead animal, unless performed soon after death, although the intestines may continue to move for a long time.

In another experiment I divided with fine scissors, at a little distance from the intestine, all the visible branches of nerves in a portion of mesentery corresponding to an inch and three-quarters of the gut, leaving the vessels uninjured. No effect was produced on the peristaltic movements, which happened to be pretty active at the time, and continued the same at the seat of the operation as elsewhere. To ascertain whether the division of the nerves had been thoroughly effected, I now transmitted powerful galvanic currents through the spine, as in former experiments, when all movements ceased in the intestine, except in the small piece whose nerves had been cut, which continued in vigorous action as before. The persistence of the vermicular motion after complete division of the mesenteric nerves shows that the movement which occurs during life, like that which takes place post mortem, is effected by a mechanism within the intestine; and its continuance in the portion of gut so treated, while other parts were relaxed, on the application of galvanism to the spine, proves that the inhibiting influence acts through the mesenteric nerves, whose integrity is necessary to the effect.

This being established, it follows that if a quiet state of the intestine, such as very frequently occurs in its natural condition, were due to a controlling agency on the part of the so-called 'inhibitory system', the complete division of the mesenteric nerves supplying a portion of gut which is at rest, would liberate it from this restraint, and movement would be the result. I performed the operation in one case under such circumstances, but the portion of intestine concerned remained as tranquil as the rest.

[1] Henle and Pfeufer's *Zeitschrift*, 2nd series, vol. viii.

To sum up the above, it appears that the intestines possess an intrinsic ganglionic apparatus which is in all cases essential to the peristaltic movements, and, while capable of independent action, is liable to be stimulated or checked by other parts of the nervous system ; the inhibiting influence being apparently due to the energetic operation of the same nerve-fibres which, when working more mildly, produce increase of function.

After the above conclusions had been arrived at, my attention was directed by Professor Goodsir to a paper by Dr. O. Spiegelberg, published last year, in which he shows that the movement of the intestines is increased by mechanical irritation of the cord. His results are particularly satisfactory, as having been obtained incidentally during an inquiry into the movements of the uterus, and so without any preconceived theory.[1] Spiegelberg also attributes the increased peristaltic action after death to arrest of the circulation, having found that the same thing occurs during life when the aorta or vena cava is compressed above the origin of the mesenteric vessels.

To proceed to the experiments upon the cardiac movements : some of these consisted in irritation of the vagus in rabbits, and this was followed by different results in different instances : thus, on one occasion the pinching of the cardiac end of the left nerve, divided in the neck, was followed by considerable increase in the number of beats as felt through the walls of the chest, but similar treatment of the right nerve afterwards caused great depression of the heart's action. Again, in one animal the evidence obtained from mechanical irritation of the vagus was almost entirely negative. In another case, the left vagus having been exposed, feeble galvanic currents transmitted through the nerve, isolated by a plate of glass placed beneath it, were succeeded by slight increase in the number of contractions. The strength of the battery having been then increased by introducing the rods into the helix, it produced first irregularity, and then complete arrest of the action of the heart, which had been previously exposed. No sign of recurrence of contraction appearing, I filled the jar to the top with acid solution, and sent powerful currents through the vagus, with the instantaneous effect of reviving the action of the heart, which, on their immediate discontinuance, continued to beat, though feebly, for several minutes. During this time I again applied the galvanism very mildly, and the result was great increase in the number of beats on several successive trials. The apparent discordance of these facts is, I believe, partly owing to differences in the state of the nerves in different cases as respects irritability and exhaustion, as will be better understood from the sequel ; and, on the whole, the experiments appear to show that, in a healthy state of the nervous system, very gentle irritation of

[1] Henle and Pfeufer's *Zeitschrift*, 3rd series, vol. ii, part 1.

the vagus increases the heart's action, while a slightly stronger application diminishes the frequency and force of its contractions. This conclusion is in harmony with an observation which I made incidentally upwards of a year ago, that irritation of the posterior part of the brain of a frog with a fine needle was repeatedly followed by improvement in the circulation, whereas it was by the application of a stronger stimulus, that of galvanism, to the same part of the cerebro-spinal axis that Weber first induced an inhibitory action on the heart.

It is said, on apparently good authority,[1] that division of the vagus in mammalia is invariably followed by increase of the action of the heart ; this, if true, would be a strong ground for believing in an inhibiting influence constantly operating upon it through this nerve. But it is also stated that the same thing does not occur in frogs ; and this circumstance appeared to me to throw much doubt upon the evidence regarding mammalia. I therefore made careful experiments on the effects of cutting both vagi, once upon a calf and four times upon rabbits, taking the number of the heart's beats immediately before and immediately after section of each nerve by the momentary stroke of a sharp pair of scissors. In no case was the rate increased at all by the operation, and the very gradual diminution in frequency that commonly took place appeared to depend on general exhaustion from other circumstances attending the experiment. In one rabbit, in which I had removed the skin and pectoralis major from the praecordial region, so as to see the movements of the heart distinctly through the transparent pericardium and intercostal muscles, I noticed particularly that the strength of the contractions, as well as their frequency, remained quite unaffected by the division of the vagi. From these facts I feel warranted in concluding that, whatever may occur under exceptional circumstances, there is certainly no constant control exercised over the heart's action through those nerves.

The influence of the spinal system upon the heart is, however, very apparent after a struggle, which almost invariably increases the frequency and force of the beats ; and I found that this continued to be the case after division of both vagi, implying that those nerves are not the only channels through which this influence is transmitted. A new field of investigation was thus opened. For, supposing the inhibitory agency to be simply the greater action of an ordinary nerve, it would probably not be exercised exclusively by the vagus, but also by the other nerves connecting the cerebro-spinal axis with the cardiac ganglia, viz. the sympathetic branches in the neck ; in which case the action of the heart should be increased or diminished, according to the strength of the stimulus,

[1] Pflüger, op. cit.

by the application of galvanism to the cervical region of the spine after the pneumogastric nerves had been cut.

In an experiment performed with this view, the poles having been fixed to about the fourth cervical and fifth dorsal spinous processes, and both vagi divided in the neck, galvanic currents only just perceptible to the tip of the tongue were first transmitted. This excessively feeble action of the battery, though apparently not very favourably situated for influencing the cord, produced marked effects upon the heart's action, increasing the number of beats, which were about forty in ten seconds, by from three to ten in that period. This effect having been observed for a considerable time, the rods of soft iron, which had been till then only inserted half-way in the helix, were pushed fully in. The battery, thus strengthened, instead of increasing, as before, the rate of the pulsations, diminished it by two in ten seconds on several successive trials. On again half withdrawing the rods, the galvanism, when applied, again increased the number of beats. A little more of the acid solution was afterwards poured into the jar of the battery, when the stronger currents which it produced reduced the number by about five in ten seconds.

Yet distinct as was this inhibiting influence, the shocks were still quite tolerable to the tongue even when the rods were fully in the helix.

These results were of great interest, as proving how slight an increase of the feeble stimulus which promoted the action of the heart sufficed to produce the opposite (inhibiting) effect. But it was by no means clear that the influence had not been exerted through cardiac branches arising from the vagi above the parts where they were divided, or even through the trunks of those nerves, which might possibly have been affected by the galvanism acting through the superjacent spinal column. In order to eliminate the vagi completely, I divided in another rabbit all the soft parts in front of the spine, except the trachea and oesophagus, at the level of the cricoid cartilage, having previously cut each carotid artery between two ligatures. The incisions were carried fairly down to the bodies of the vertebrae, and outwards beyond the tips of the transverse processes, so as to ensure the section not only of the vagi and their branches, but also of the sympathetic cords, with any filaments of those nerves which they might contain. Also the poles of the battery were fixed to the spinous processes of the seventh dorsal and first lumbar vertebrae, so as to avoid all possibility of direct action of the galvanism upon either the vagi or other cardiac nerves. Feeble currents being then transmitted, diminution of the number of beats to the extent of two to four in ten seconds occurred in several successive trials, the results being so constant as to leave no doubt that they were produced by the galvanism.

It may appear almost incredible that such extremely mild galvanic currents, applied through the spinous processes of the posterior dorsal region, should be capable of thus affecting the heart; but that their effects were really very considerable, was clear from the further progress of this experiment, and from others somewhat similar, which showed that this apparently trivial stimulation gradually exhausted the part of the nervous system through which the heart is acted on by the cord. Thus, in one case, currents only just perceptible to the tongue, transmitted for about thirty seconds at a time through the lower cervical and upper dorsal regions of the spine, at intervals of nine minutes on the average during two hours and twenty minutes, produced at first decided increase of the heart's action, but during the last hour failed to affect it at all. The strongest possible action of the battery which, as proved by other experiments, would, at the outset, have entirely arrested the cardiac movements, was then set on, but with no effect whatever on the organ.

When partial exhaustion has occurred, a much stronger galvanic stimulus is required, to produce the same effect upon the heart, than at the commencement of an experiment; and thus an action of the battery which, when first applied, causes marked diminution in the number of beats, may after a while come to have the opposite effect, and increase the heart's action as decidedly as it had previously lowered it; while at an intermediate period it may seem to have no influence at all. This principle gives the clue to understanding what had before appeared incomprehensible in these experiments, showing that facts, which at first seemed utterly inconsistent, were really perfectly harmonious. The case before related, in which revival of the heart's action resulted from powerful stimulation of the vagus, which, had the organ been contracting as usual, would have arrested its movements and probably finally destroyed them, will now be understood. I have seen other analogous cases of revival of action by very powerful galvanism, which under ordinary circumstances would have arrested it, viz. twice in the heart and twice in the intestines. The observation published so long ago as 1839 by Valentin,[1] that mechanical or chemical irritation of the vagus in the neck of an animal recently dead, and with the nerves consequently enfeebled, causes contraction of the ventricles, admits of a similar interpretation, as also does a corresponding fact regarding the splanchnic nerves, given without explanation by Kupfer and Ludwig, in a paper just published,[2] viz. that they lose their inhibitory influence a certain time after death, and acquire a motor power over the intestines.

Two more experiments require mention, as they exclude the possibility of

[1] Valentin, *De Functionibus Nervorum*, p. 62.

[2] Henle and Pfeufer's *Zeitschrift*, 3rd series, vol. ii, part 3.

the agency in them of either the vagi or the part of the brain from which the vagi spring, having been performed upon decapitated rabbits. In one of these cases, the carotids having been tied near the head, the neck was completely severed behind the first vertebra, care being taken to avoid haemorrhage from the vertebral arteries, and artificial respiration, for which provision had been made, was carried on for an hour and a half after decapitation. The results of moderate galvanism, applied to the posterior dorsal region of the spine, to which the poles had previously been attached, were at first not distinct, but afterwards decided increase of action was produced by it when applied at intervals during half an hour, the effect being perfectly apparent in the heart which lay exposed before me. Exhaustion of the nerves concerned having then taken place, the most powerful action of the battery failed to influence the character of the contractions.

In the other case, the poles having been fixed as before, and the head similarly removed, powerful galvanic currents were immediately transmitted. The pulsations of the heart in the opened chest at once fell from thirty-five to sixteen in ten seconds, but rose again to twenty on the removal of the stimulus.

Hence it is clear that the sympathetic branches connecting the cord with the cardiac ganglia have equal claims with the vagi to be called 'inhibitory nerves'. In fact this expression seems to me altogether objectionable, since there is good reason to think that the same fibres which check the movements much more commonly enhance them. The only evidence afforded by my experiments that the inhibiting influence is ever exerted in the natural actions of the animal consisted in the quiescence of the intestines sometimes seen after a struggle, and two doubtful observations of retardation of the heart's beats from the same cause. Indeed it appears very questionable whether the motions of either of these viscera are, under ordinary circumstances, ever checked by the spinal system, except for very brief periods; whereas the increased action of both heart and intestines, familiarly known to result from mental emotion, may last for a very considerable time. The fact that the nerves of these organs are capable of setting them at rest under conditions of extraordinary irritation is nevertheless a matter of great importance, especially in a pathological point of view, and appears to afford an explanation of facts in medicine hitherto little understood—such as failure of the heart's action from violent emotion or pain, and the constipation which attends strangulated omental hernia.

From the observations of Spiegelberg,[1] it would appear that the uterine contractions are promoted by mechanical irritation of the cord, and arrested by transmitting a powerful stream of galvanism through the spine. Also the forcible

[1] Henle and Pfeufer's *Zeitschrift*, 3rd series, vol. ii, part 1.

expulsion of urine very frequently seen in the lower animals in consequence of fear, and the temporary palsy of the detrusor often witnessed in the human subject in surgical practice as the result of severe injury, seem to me to imply that the bladder, too, while sometimes stimulated through the cerebro-spinal axis, is paralysed by its very powerful operation. Hence it seems probable that the movements of all the hollow viscera are liable to similar influence from the spinal system. At the same time it appears to be a mistake to regard this influence in the light of a strict control; for the experiments related in this letter show pretty distinctly that the contractions of the heart and the peristaltic action of the intestines are regulated, under ordinary circumstances, by the independent operation of the intrinsic ganglia.

Professor Schiff has, I understand, observed increase of the heart's action to result from very gentle stimulation of the vagus,[1] and has come to the conclusion, as stated by Spiegelberg in his paper before referred to, that the inhibiting influence depends upon nervous exhaustion. There are some circumstances which make me entertain great doubt as to the correctness of this view. In the first place, the very rapid recovery of the cardiac or intestinal actions when the inhibiting galvanic currents are discontinued, contrasts strongly with the length of time that the impairment of function resulting from a protracted experiment, and certainly due to exhaustion, lasts both in the intrinsic cardiac nerves and in those that connect them with the spinal system. Secondly, although very powerful galvanism not only arrests for the time, but permanently impairs the action of the heart, no such effect is observed to follow the inhibiting influence when it is caused by milder stimulation; indeed, according to my experience, less injurious effects are produced upon the heart by a protracted series of experiments of the latter kind than by a corresponding set with the currents still more feeble, that increase, while acting, the frequency of the contractions. But if the diminished rate of the pulsations were caused by a partial exhaustion of the cardiac ganglia, an opposite result might have been anticipated.

Again, there can be little doubt that dilatation of the blood-vessels, in consequence of a stimulus, is due to an effect produced upon the nervous centres for the arteries, similar to that experienced by the visceral ganglia when subject to the inhibiting influence. Now an inflammatory blush of long continuance may subside rapidly when the source of irritation is withdrawn. Thus I have seen redness which had existed for about three days in the human skin in consequence of tight stitches connecting the lips of a wound, give place at once to pallor on their removal. Had the arterial dilatation in this case been the

[1] Henle and Meissner's *Bericht*, 1857.

result of nervous exhaustion continued during so long a period, such speedy recovery could hardly, one would think, have taken place.

These and other considerations, to which the already excessive length of this letter forbids me to allude, induce me to think it safest in the present state of science to regard as a fundamental truth not yet explained, that one and the same afferent nerve may, according as it is operating mildly or energetically, either exalt or depress the functions of the nervous centre on which it acts. It is, I believe, upon this that all inhibitory influence depends, and I suspect that the principle will be found to admit of a very general application in physiology.

I am, &c.,

JOSEPH LISTER.

SOME OBSERVATIONS ON THE STRUCTURE OF NERVE-FIBRES

WRITTEN IN COLLABORATION WITH WILLIAM TURNER[1], ESQ., M.B., Lond.,
Senior Demonstrator of Anatomy in the University of Edinburgh.

[*Quarterly Journal of Microscopical Science*, October 1859.]

HAVING recently had the opportunity, through the kindness of Mr. Lockhart Clarke, of inspecting some of his beautiful preparations of the spinal cord, we were struck with an appearance which had not yet received a satisfactory interpretation; and, having been induced to investigate the point, we have met with some facts which seem of sufficient interest for publication.

For the sake of clearness it may be well to state briefly the method employed by Mr. Clarke in preparing his specimens.

A portion of perfectly fresh spinal cord having been hardened by steeping in dilute chromic-acid solution, thin sections are made with a razor, and these, after immersion for a while in an ammoniacal solution of carmine, are soaked in spirits of wine to remove the water, and then treated with oil of turpentine. The last-named agent has the effect of rendering the sections transparent, so that the nerve-cells of the grey matter, finely coloured by the carmine, are seen with the utmost distinctness, giving off in various directions long branching processes; while the nerve-fibres, which are similarly tinted, may be traced with equal facility in their course through the cord.

In the preparations which we saw, the cord had been sliced crosswise, and in the columnar regions, where the nerve-fibres have for the most part a longitudinal direction, the transverse section of each fibre showed itself as a carmine-coloured point, surrounded by a perfectly pellucid and colourless ring. This was the appearance which seemed to demand explanation, the question being whether the transparent ring was a mere space, resulting from shrinking of the object during the preparation, or the white substance of Schwann (medullary sheath) rendered transparent by the turpentine, the axial cylinder alone, in that case, having received the carmine colour.

It occurred to us that the point might probably be determined by applying a similar mode of preparation to some nerve the dimensions of whose fibres could be readily ascertained. With this view we steeped in chromic acid portions of the sciatic nerve of a cat just killed, and also parts of the spinal cord of the

[1] Now (1908) Sir William, K.C.B., F.R.S., Principal and Vice-Chancellor of the University of Edinburgh.

same animal; and having allowed them to remain between three and four weeks in the solution, we commenced the investigation in July of the present year, 1859.

A transverse section of the hardened sciatic nerve having been placed for a time in the carmine solution and then dried, we submitted it, without the application of turpentine, to microscopic examination with a power of 130 diameters. Viewed by transmitted light, it appeared as a confused opaque mass; but, by reflected light, it exhibited the structure depicted in Plate IV, Fig. 1,[1] each nerve-fibre presenting in its section a carmine spot, surrounded by a yellowish-white, somewhat granular ring, which, though doubtless corresponding to the pellucid rings in the preparations of the cord before alluded to, was clearly composed of some solid material, in short, of the white substance of Schwann altered by the action of the chromic acid.

We next examined sections of the cord treated in the same way, but found that these dry specimens were so incrusted with carmine that they gave no definite results. It happened, however, that one of the sections treated with carmine still remained moist, and, after washing away all superfluous colouring matter, we examined it by transmitted light. A very beautiful appearance now presented itself, carmine points being seen in the columnar regions, as in Mr. Clarke's preparations, surrounded by rings; but the latter, instead of being transparent like mere spaces, were dead white; the carmine points, on the other hand, appearing in the thinnest parts of the section as illuminated spots amid the general opacity. This is represented in Fig. 5.

It will be seen from this sketch, which is drawn on the same scale as Fig. 1, that the nerve-fibres varied very much in their diameter, the largest being of about the same size as those of the sciatic nerve, while others were of extreme minuteness; but in all cases in which they were sufficiently large to be distinguished, they had the same character of a white circle with a central carmine spot from one-fourth to one-third the diameter of the whole fibre. It was obvious that, in the cord, as in the sciatic nerve, the carmine central part of each fibre was the axial cylinder, and the opaque circumferential portion the medullary sheath; and, therefore, that the pellucid rings in preparations treated with turpentine consisted of the white substance rendered transparent by that reagent.

The point at issue was thus satisfactorily decided; but for the sake of confirmation we made some further observations, the results of which seem deserving of mention.

On examining the hardened sciatic nerve, without tinting the preparations

[1] This sketch, like the others illustrating this paper, was drawn by means of the camera lucida.

with carmine, we found that in extremely thin slices the transverse sections of the nerve-fibres, viewed by transmitted light, appeared as brownish rings with central transparent colourless spots (see Fig. 3), whilst by reflected light the central parts appeared black, as shown in Fig. 2. In fact, under a low power the axial cylinders had, in these specimens of the sciatic nerve, as much the appearance of mere spaces as the medullary sheaths had in preparations of the cord treated with turpentine. But on applying a fine glass of high power a granular appearance was disclosed in the pellucid central portion, showing that it was in reality a solid substance, though of a transparency which was very remarkable, considering that it had been so long subjected to the action of chromic acid ; and on afterwards treating similar sections with carmine we found that this part alone became coloured. The higher magnifying power also brought out an appearance of irregular concentric lines in the brown[1] medullary sheath ; and this, together with the granular aspect of the axial cylinder, is represented in Fig. 4.

These facts afford a very striking illustration of the essential difference in chemical composition between the axial cylinder and the medullary sheath, the former being totally unaffected by chromic acid, though the latter is rendered opaque and brown and concentrically striated under its influence, while, on the other hand, the axial cylinder, after being subjected to the action of chromic acid, imbibes the carmine colour with peculiar facility, although the medullary sheath is entirely untinged by it.[2]

We next applied the high magnifying power to extremely thin slices of the spinal cord prepared in the same way. In transverse sections of the columnar regions the white substance of Schwann presented, in the larger fibres, the same concentrically arranged appearance as we had observed in the sciatic nerve, as is illustrated by Figs. 6 and 7, of which Fig. 6 is one of the largest met with, being 1-900th of an inch in diameter, while Fig. 7 is as small as 1-3000th of an inch in transverse measurement. In the very minute fibres no appearance of concentric lines could be detected, yet, wherever the existence of an axial cylinder was indicated by a carmine point, a ring of medullary sheath was always visible, presenting the same proportion to the axial cylinder as in fibres of larger size. This may be gathered from Figs. 8, 9, and 10, of which Fig. 8 measures 1-5000th of an inch across, Fig. 9 1-8000th, and Fig. 10 only 1-14000th.

[1] It must be mentioned that a similar brown colour is seen in the superficial parts of a cord which has been steeped in chromic acid, but the deeper portions of the organ are comparatively only slightly coloured, so that in individual nerve-fibres seen under a high magnifying power the brown tint is not observed.

[2] In a boiled fresh nerve also the medullary sheath remains unaffected by ammoniacal solution of carmine, while the axial cylinder assumes a distinct though very faint pink tint.—J. L.

At the margins of longitudinal sections of the cord, the contrast, both in structure and in tint, between the axial cylinder and the medullary sheath showed itself very beautifully. It often happened that a projecting isolated fibre was, near its extremity, more or less divested of the white substance of Schwann, so that the delicate, carmine-tinted axial cylinder was exposed, though presenting here and there colourless flakes of the medullary sheath adhering to its surface, while in parts where the nerve was still entire, the pink colour of the central fibre could be distinctly discerned through the intervening white substance. Fig. 11 represents a large fibre under such circumstances, and Fig. 12 one of considerably smaller size ; and these sketches also display the remarkable fibroid arrangement which we find the white substance of Schwann invariably assumes under the influence of chromic acid.

In conclusion, we may remark that the successive employment of chromic acid and carmine seems likely to afford valuable aid in discriminating nerve-fibres among other structures, there being, so far as we are aware, no other form of tissue which, after the use of these means, exhibits fibres having a central carmine axis and peripheral uncoloured sheath.

Supplementary Observations by Mr. Lister

The fibroid arrangement of the white substance of Schwann in nerves hardened by chromic acid has been minutely described by Stilling, in his elaborate treatise on the ' Nerve-fibre and Nerve-cell ',[1] a work which we had not seen when the foregoing communication was written, but a copy of which was kindly lent me by Professor Goodsir, soon after Mr. Turner had left Edinburgh for the vacation. According to Stilling, the medullary sheath is, even in perfectly fresh nerves, composed of a network of fibres, which are continuous with others in the axial cylinder and in the proper investing membrane ; so that, in his opinion, these three constituents of the nerve-fibre differ from each other only in the manner in which their elements are disposed.[2] This view is not only quite novel anatomically, but is opposed to the generally received physiological opinion, that the axial cylinder is the essential part of the nerve-fibre, and the medullary sheath an insulating investment. Considering the high estimation in which the writings of Stilling on the anatomy of the nervous centres are deservedly held, and the influence which therefore attaches to his opinions, it seems fortunate that we have been able to present so clear a demonstration that the axial cylinder is chemically as well as morphologically totally distinct from the medullary sheath.

[1] *Ueber den Bau der Nerven-Primitivfaser und der Nervenzelle.* Von Dr. B. Stilling. 1856.
[2] Op. cit., p. 6.

With regard to the cause of the fibroid arrangement of the medullary sheath, an observation which I happened to make several years ago, regarding the aggregation of fatty matter, may perhaps tend to throw light upon the subject. I submitted to microscopic examination some of the pultaceous slough of a sore affected with hospital gangrene, thinking it possible that I might discover in it some fungus which might account for the peculiar specific character of that disease; and found in it numerous bodies, each composed of branching fibres radiating from a common centre, and looking, at first sight, like some sort of vegetable growth, so that I made careful sketches of them, one of which is reproduced in Fig. 13. But seeing afterwards, in the same object, some bundles of acicular crystals of margarine having a distant resemblance to the bodies I had drawn, I added ether to the specimen, and found that it dissolved the latter equally with the former. This showed that what first attracted my attention was merely an arborescent form of aggregation of some fat, probably margarine; and it seems not unlikely that the fluid fat which exists in the medullary sheath of a perfectly fresh nerve may tend to a similar arrangement of its particles when passing into the solid form, and so give rise to the appearance in question. It is to be remarked that the fibroid character is not peculiar to specimens treated with chromic acid, but also shows itself, though in a less perfect manner, in nerves which have been subjected to other modes of preparation—for example, after exposure for a few seconds to a temperature of 212° Fahr.

There is another important statement made by Stilling, which the use of the method of examination above described enables me to correct. He speaks of the fibres which connect one nerve-fibre with another as similar in every respect to those seen in the medullary sheath.[1] I find, however, that both in the sciatic nerve and in the spinal cord of the cat, the connective tissue between the nerve-fibres, like the neurilemma and pia mater, with which it is continuous, becomes coloured by the carmine; whereas, the medullary sheath, as before stated, is quite unaffected by it, proving that the two structures are chemically distinct from one another. In both these situations, too, the fibres of the connective tissue are much more delicate than the constituents of the medullary sheath, which are often comparatively coarse, as may be seen from Fig. 11. In the columnar regions of the cord, the former require a high magnifying power to be applied to very thin sections, in order to distinguish them, and are often present in such extremely small quantity that, without very careful examination, the nerve-fibres appear actually in contact with one another. In the sciatic nerve I have observed occasional elongated nuclei in the connective tissue.

[1] Op. cit., p. 7.

I may add that glycerine has proved very useful, not only for permanently preserving the preparations in the moist state, but also as an aid to investigation; for it renders the sections much more transparent, without making the white substance of Schwann invisible, as turpentine does ; and hence the course of the nerve-fibres through the cord can be traced much more easily, and, at the same time, the proportion between the medullary sheath and axial cylinder can be readily ascertained. Thus, by examining transverse sections of the cord in this way, I find that while Kölliker is quite correct in his statement that the fibres of the roots of the nerves diminish in size in passing inwards through the columnar regions,[1] yet the diminution affects only the white substance, the axial cylinder often retaining its full dimensions even in the middle of the grey matter, while the medullary sheath is reduced to a very thin crust, so that the nerve-fibre assumes a character differing but little from that of an offset of a nerve-cell.

[1] Kölliker's *Handbuch der Gewebelehre*, 3rd ed., p. 285.

DESCRIPTION OF PLATE IV

Fig. 1 represents part of a transverse section of the sciatic nerve of a cat hardened by chromic acid, and tinted with carmine, the axial cylinder alone having received the colouring matter. The specimen was dried and viewed as an opaque object.

Fig. 2 shows the appearance of thin transverse sections of some nerve-fibres from the same nerve, simply hardened in chromic acid, and examined moist by reflected light. The axial cylinder has, under this low magnifying power, the aspect of a mere space.

Fig. 3, similar objects to those of Fig. 2, but seen by transmitted light.

Fig. 4, a highly magnified transverse section of a nerve-fibre from the same source, prepared like those of Figs. 2 and 3, and then tinted with carmine. The carmine colour is seen to affect only the axial cylinder and the investing membrane, which, at one part, is torn up from the fibre. This sketch also shows the faintly granular structure of the axial cylinder, and the irregularly concentric striation of the medullary sheath.

Fig. 5, a transverse section of a columnar portion of the spinal cord of a cat, also prepared with chromic acid and carmine, and examined moist by transmitted light. The fibres vary much in size, but all of them resemble those of the sciatic nerve in having the red axial cylinder surrounded by a ring of untinted medullary sheath.

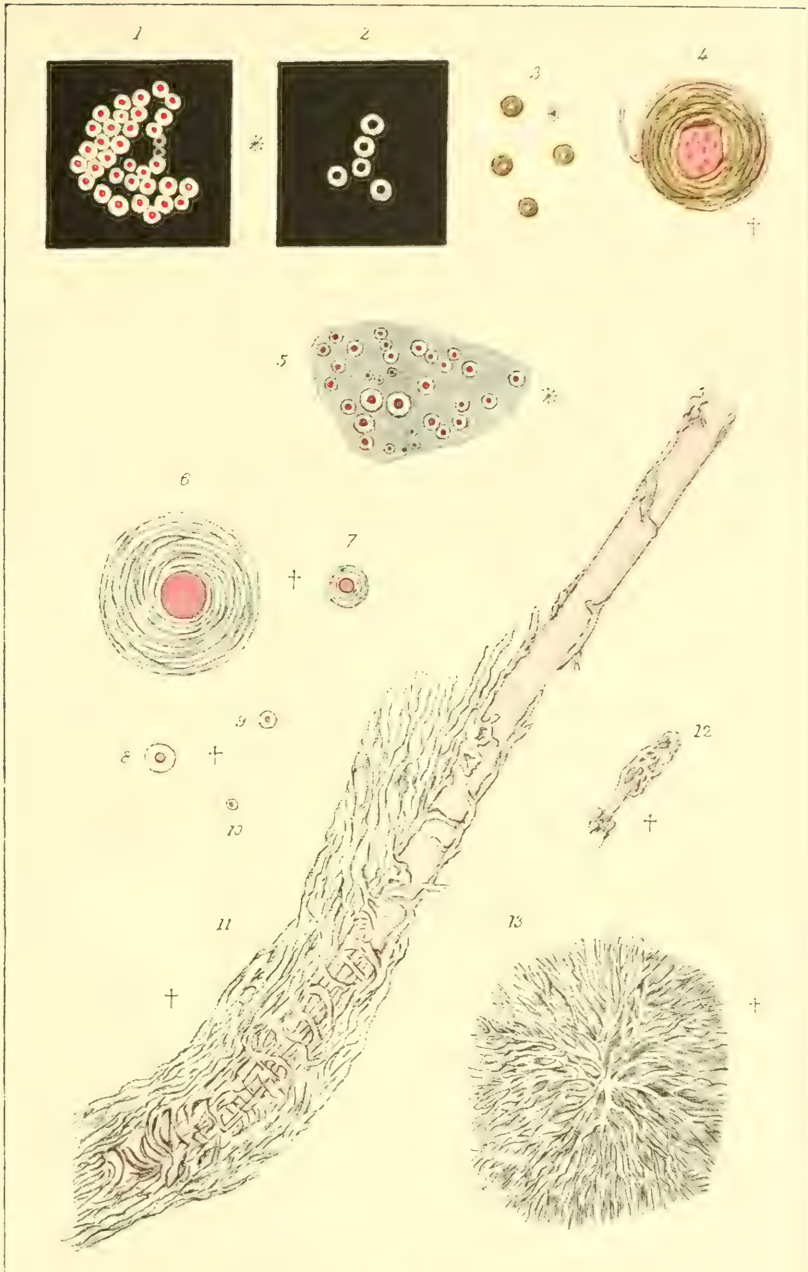
Figs. 6–10 are highly magnified views of some fibres in a section of the cord like that of Fig. 5. They present the same characters as the fibres of the sciatic nerve.

Fig. 11, a fibre from a longitudinal section of a columnar portion of the cord, prepared in the same way The axial cylinder alone is carmine coloured, and is, in some parts, stripped of its investing sheath, the fibroid arrangement of which is also displayed.

Fig. 12, a small fibre under similar circumstances.

Fig. 13, fatty matter in a state of arborescent fibroid aggregation.

Plate IV



* 730 diameters
† 750

NOTICE OF FURTHER RESEARCHES ON THE COAGULATION OF THE BLOOD

Read before the Medico-Chirurgical Society of Edinburgh, November 16, 1859.

[*Edinburgh Medical Journal*, December 1859.]

Mr. President.—I take this opportunity of demonstrating what appears to be a point of considerable importance with reference to the coagulation of the blood—a subject to which my attention has been again directed by the recurrence of that period of the Session in which the fundamental principles of pathology are discussed in a course of surgical lectures.

I may remind the Fellows of this Society, that in a paper which I had the honour to read before them the Session before last,[1] I brought forward facts which seemed to prove that the ammonia theory does not apply to blood within the vessels of a living animal. That theory, as my hearers are doubtless aware, asserts that the fluidity of the blood depends upon the presence of a certain amount of free ammonia holding the fibrine in solution, and that coagulation is the necessary result of the escape of the volatile alkali. But it was shown in the paper referred to, that the blood, in man and other mammalia, though coagulating soon after death in the heart and great venous trunks, remains fluid for days in vessels of smaller size, and this under circumstances affording free opportunity for the escape of ammonia; and, on the other hand, that when a portion of a vessel either in an amputated limb or in a living animal is treated in a manner calculated to destroy its vital properties, the blood coagulates in the injured part, but retains its fluidity elsewhere, although there is no greater opportunity for the escape of ammonia in the one case than in the other. A striking instance of the difference between the natural receptacles of the blood and ordinary matter in their relations to the vital fluid happened to come under my notice this morning, in an arm which I amputated last evening at the shoulder-joint, on account of injury inflicted by machinery. On examining the limb, which had lain undisturbed since the operation, I saw that the axillary vein, which was patulous at the part where it had been divided by the knife, contained some blood at a distance of about half an inch from the open orifice; and having squeezed out a few drops, found that it was perfectly fluid, but yielded threads of fibrine when the point of a needle was drawn through it some minutes after emission. The blood had been for upwards of twelve

[1] Vide *Edinburgh Medical Journal*, April 1858 (p. 69 of this volume).

hours freely exposed to the air, but being situated in an uninjured part of a blood-vessel, had remained free from coagulation.

Further, in the opening meeting of last Session I demonstrated another important principle, viz.—That ordinary solid matter, unlike atmospheric air, induces coagulation of blood in its vicinity when introduced within the living vessels. Having inserted a piece of clean silver wire for a considerable distance into one of the veins of an amputated sheep's foot, I slit up the vessel after a short time had elapsed; when I exhibited a coagulum extending along the whole length of the foreign body, whereas a mere wound of the vein failed to induce a clot except immediately at the spot where the injury had been inflicted. It was obvious that the introduction of the wire could not affect the amount of ammonia in the blood; and from this and many other facts, to which I need not here allude,[1] I was led to the opinion, that as regards what takes place within the living vessels, the ammonia theory might practically be left entirely out of consideration.

What I have to show this evening will, I think, prove that even for blood outside the body, the ammonia theory, whatever degree of truth it may contain, is very far indeed from representing the whole truth.

One of the most remarkable circumstances connected with blood that has been shed from the vessels is, that it refuses to coagulate below a temperature of 40° Fahr. or thereabouts. This is explained by Dr. Richardson on the hypothesis that the low temperature prevents the evolution of ammonia,[2] while the rapidity with which coagulation takes place at high temperatures seems to him satisfactorily accounted for by the increased volatility exhibited by the ammonia under such circumstances. I was myself at first disposed to accept this interpretation, but subsequent reflection led me to think that, to say the least, it required confirmation. It occurred to me that if it were true that the fluidity of blood below 40° was due to free ammonia retained in it, coagulation would take place immediately, in spite of the cold, if the alkali were neutralized by the addition of acid, provided the fibrine were not impaired in its coagulating property by the reagent employed. In order to ascertain whether this result would really follow, I poured blood freshly shed from a sheep into vessels surrounded by ice-cold water, and by this means succeeded in keeping some portions of it fluid for a considerable time, and found that it continued liquid notwithstanding the addition of dilute acetic acid in what I supposed must be

[1] For some of these facts see 'On the Early Stages of Inflammation,' Philosophical Transactions for 1858, pp. 673, et seq.

[2] See Dr. Richardson's *Astley Cooper Prize Essay*, p. 303, where a fact is mentioned, indicating that no ammonia was given off at 34° Fahr. from a specimen of blood which had been artificially ammoniated, and which at 96° afforded distinct evidence of evolution of the alkali.

sufficient quantity to overcome the feeble alkalinity of the blood, while the acidulated specimen retained the property of coagulating very rapidly when raised in temperature. But on attempting to discover whether this blood was really acid in reaction, I found that its red colour entirely vitiated the indications of both litmus and turmeric ; and even the serum obtained after contraction of the clot was too much tinged to admit of the satisfactory application of the test-paper.

Being thus baffled in my experiments with the sheep, I had recourse to the horse, in which the red corpuscles subside with peculiar rapidity in the plasma, giving rise to the buffy coat well known to occur in the blood of that animal in the state of health, so that the opportunity would be presented of obtaining liquor sanguinis free from red corpuscles, to which the tests could be applied without risk of fallacy. Accordingly, yesterday afternoon, a horse having been placed at my disposal by my friend Mr. Gamgee of the New Veterinary College, I tied into the right jugular vein one end of a piece of vulcanized india-rubber tube, four yards in length, the greater part of which was coiled up in a freezing mixture, and some of the blood, having been allowed to remain for a while in the tube, was shed into vessels standing in ice-cold water. Its temperature on first escaping into the air was $39\frac{1}{2}°$ Fahr., and having been since kept in the cold it is still only partially coagulated at the present time (twenty-nine hours after it was shed). At first, however, it appeared as if we were likely to fail, the blood of this horse being a rare exception to the general rule, in exhibiting for a long time no appearance of the ' sizy ' layer. But after it had stood for about two hours, I succeeded in removing from the surface, by means of a glass tube, a sufficient amount of liquor sanguinis for the performance of an experiment, taking care that the glass into which it was shed, and the tube, were both near the freezing-point. To half a drachm of this plasma I now added one minim and a half of moderately dilute acetic acid, which had the effect of rendering it distinctly acid, as indicated by its communicating a red tint to litmus and restoring the colour of turmeric paper which had been reddened by dipping it in the portion of the liquor sanguinis which had not been acidulated. I kept the specimen in ice-cold water till this evening. For a long time it remained perfectly fluid, except the formation of little soft coagulum at the surface, just as in the unacidulated blood ; but a few drops placed in a watch-glass and brought into a warmer atmosphere, coagulated in about the same time as the blood that first flowed from the tube, a soft clot forming in about a quarter of an hour. Even at the expiration of twenty-four hours a portion of what remained in the cold was still fluid, though faintly acid, but set into a pretty firm clot on being removed into a warmer situation.

[Mr. Lister now proceeded to perform a similar experiment before the Society. A glass containing some liquor sanguinis of the horse's blood, shed twenty-nine hours before, was taken out of the mixture of ice and water in which it stood, and the contents were seen to be still to a considerable extent fluid, although acidulated with acetic acid two hours previously. A portion of the liquid was poured into a watch-glass, and, having been shown to be acid by litmus paper, was set aside to coagulate, and about a quarter of an hour later was exhibited as a soft clot. Mr. Lister then continued :—]

From these facts it is obvious that the ammonia theory utterly fails to explain the influence of temperature on coagulation. The circumstance that the liquor sanguinis was acid in this experiment is clear proof that it contained no free ammonia whatever, yet the acidulated plasma was affected by cold and heat, just like ordinary blood. It remained fluid near the freezing-point, although the ammonia it originally contained must have entered into combination and lost its reputed power of dissolving the fibrine, and it coagulated when warmed, though the ammonia, fixed by the acid, must have been incapable of evolution. If the author of the ammonia theory were asked to explain why this horse's blood took a quarter of an hour to coagulate, he would no doubt reply that it must have contained a large amount of ammonia, requiring all this time to escape. But we have seen that the acid liquor sanguinis, though possessing no free ammonia at all, took as long to clot. There can therefore I think be little question but that the slowness of coagulation in the horse, compared with the rapidity of the process in the sheep, and the variations met with in the period in the human species, depend not on the amount of ammonia present in the blood, but on differences in its other constituents, and, speaking generally, that the theory which attributes the coagulation of the blood to the escape of ammonia is fallacious.[1]

[1] Since the above communication was made, I have seen for the first time the able essay of Dr. E. Brücke, which competed for the Astley Cooper Prize (see *Med.-Chir. Review*, vol. xix) ; and I find that the principle which he advocates—viz. that the fluidity of the blood within the living body depends upon an action of the walls of the vessels upon it—is supported by many facts which he has observed in the chelonian reptile, very similar to what I have made out in mammalia. Thus, he found that the blood remained fluid in the heart of the turtle for days after death, and for several hours after he had blown air through the veins of the neck, so as to make a foamy mixture in the cavities of the organ. He also found, as had been previously ascertained by Virchow and others, that after the introduction of mercury into the heart the blood coagulated about the globules of the metal, but not elsewhere, and this he regarded as an example of the influence of ordinary matter in inducing coagulation in its vicinity. He also succeeded with the following very striking experiment, which would not have answered with mammalia : he drew blood into a cup from the veins of a living turtle, and injected it into the empty heart of another turtle just killed, and found that the blood remained fluid for several hours in its new situation, instead of coagulating in a few minutes as when retained in a cup.—J. L.

ON THE COAGULATION OF THE BLOOD

THE CROONIAN LECTURE

Delivered before the Royal Society of London, June 11, 1863.

[*Proceedings of the Royal Society of London*, 1863.]

THE subject on which I have the honour to address you this evening is one which lies at the foundation both of Physiology and Pathology, and, on account of its great importance, has engaged the best energies of many very able men, among whom may be mentioned, for example, such distinguished Fellows of this Society as John Hunter and Hewson; so that it might well seem presumptuous in me to hope to communicate anything new regarding it, were it not that the constant progress of Physiology and the allied sciences is ever opening up fresh paths for inquiry, and ever affording fresh facilities for pursuing them. Indeed, my difficulty, on the present occasion, does not depend so much on the lack of materials as on the complicated relations of the subject, which make me almost despair of being able, in the short time that can be devoted to a lecture, to give, in anything like an intelligible form, even an adequate selection of the facts at my disposal.

It may, in the first place, be worth while, more especially for the sake of any present who may not be physiologists, to mention very briefly some well-known general facts respecting the constitution of the blood. The blood, if examined by the microscope within the vessels of a living animal, is seen to consist of a liquid and numerous small particles suspended in it. The liquid is termed the 'liquor sanguinis', the particles the 'blood-corpuscles'. Of these corpuscles a few are colourless, and are named the 'colourless' or 'white corpuscles'. The great majority are coloured and cause the red appearance of the blood, and hence are called the 'red corpuscles'. Soon after blood has been shed from the body, it passes from the fluid into the solid form. This depends upon the development in the blood of a solid material termed 'fibrine', so called from its fibrous nature, consisting, as examined by the naked eye, of tenacious fibres, and having the same character also under the microscope. These fibres form a complicated network among the blood-corpuscles, and from their tenacity are the cause of the firmness of the clot. Soon after the process of solidification or coagulation is complete, the fibrine exhibits a disposition to shrink, and squeezes out from among the corpuscles entangled in its meshes a straw-coloured fluid termed the serum, very rich in albumen, in fact very similar in chemical composition to the fibrine, which, in its turn, may be said to be identical chemically with the material of muscular fibre.

The question before us, therefore, is, What is the cause of the development of this solid material, the fibrine ? The subject may be looked at in two aspects—first, as to the essential nature of the process of coagulation ; and secondly, as to the cause of its occurrence when the blood is removed from the body.

With regard to the first point, the essential nature of the process of coagulation, different views have been entertained. John Hunter was of opinion that the coagulation of the blood, the solidification of the fibrine, was an act of life—analogous, in some respects, to the contraction of muscular fibre. This, on the other hand, was made very unlikely by the observation of his contemporary, Mr. Hewson, that blood may be kept in the fluid state by the addition of various neutral salts, but retains the faculty of coagulating when water is added to the mixture. Mr. Gulliver, on one occasion, kept blood fluid, by means of nitre, for upwards of a year, but found that it still coagulated on the addition of water. It seems exceedingly improbable that any part of the human body should retain its vital properties after being thus pickled for more than a year. But here I would wish to make an explanation of the use of this term ‘ vital properties ’. When employing it, I do not wish to commit myself to any particular theory of the nature of life, or even to the belief that the actions of living bodies are not all conducted in obedience to physical and chemical laws. But it appears that every component tissue of the human body has its own life, its own health, just as we ourselves have ; and as the actions of living men will ever retain their interest whatever views be entertained of the nature of life, so must the actions of the living tissues ever continue to be essential objects of study to the physiologist and pathologist. When, therefore, I use the term ‘ vital properties ’, I mean simply properties peculiar to the tissues as components of the healthy living body.

Turning now to the other aspect of the subject of coagulation—the cause of the occurrence of that process on the escape of the blood from the living body—we find that here again various theories have been held, which may be divided into mechanical, chemical, and vital. The mechanical theory was, that mere rest of the blood was sufficient to cause coagulation. I say this *was* the theory ; but I believe it will be found to be still taught by many that the cause of the coagulation of the blood in an artery which has been tied is its stagnation in the vicinity of the ligature.

As to the chemical theories they have been various. One very natural view was that exposure to the air was the essential cause of coagulation. Mr. Hewson believed that this was, at all events, an important element in the causes of the phenomenon ; and many eminent physiologists and pathologists have held the same view, except that, instead of the air as a whole, the oxygen of the air has been supposed to be the important element.

Sir Charles Scudamore considered that coagulation was greatly promoted by the escape of carbonic acid ; and more recently the evolution of ammonia has been regarded as the essential cause of the change. According to the ammonia theory, due to Dr. Richardson of this city, the fluidity of the blood within the body depends on a certain amount of free ammonia holding the fibrine in solution, and the coagulation of the blood when withdrawn from the vessels is the result of the escape of the volatile alkali.

Then, as to vital theories. These have been held by many physiologists, among whom may be mentioned Sir Astley Cooper and Mr. Thackrah, who, from experiments which they performed, were led to the inference that the living vessels exert an active influence upon the blood, by which coagulation is prevented ; and Mr. Thackrah went so far as to attribute this action of the vessels to nervous influence. The view that the blood is kept fluid by the operation of its natural receptacles has been advocated more recently by Brücke of Vienna, whose essay will be found in the *British and Foreign Medical Review* for 1857. Brücke performed his experiments on turtles and frogs, in which animals the blood remains fluid in the heart for days after death ; and I feel bound to say that some of the facts which he has brought forward seem to me quite sufficient to show that the ammonia theory, whatever amount of truth it may contain, cannot be the whole truth, and cannot explain the fluidity of the blood within the body. For example, Brücke found that, having shed blood from the heart of a living turtle into a basin, and transferred, with a syringe, a portion of that blood into the empty heart of another turtle just killed, the blood thus transferred into the empty heart remained fluid for hours, whereas that which was left in the basin coagulated in a few minutes. He also found that blood continued fluid in the heart of a turtle long after the injection of air into the heart through a vein till the cavities of the organ contained a foamy mixture of blood and air.

Yet it by no means follows that the vital theory and the ammonia theory are necessarily altogether inconsistent. It might be true for anything we could tell, *a priori*, that the coagulation of the blood, when shed from the body, might depend on the evolution of a certain amount of ammonia, previously holding the fibrine in solution, and yet it might, at the same time, be true that the cause of the ammonia remaining in the blood in the healthy vessels might be an action of the living vessels retaining it there. It might be that an action of the living vessels might chain down the ammonia and prevent it from escaping, whereas, when shed from the body, it would be free to escape.

This notion was, I confess, at one time entertained by myself ; and one of my earliest experiments was performed with a view to the corroboration of the ammonia theory as applied to blood outside the body. It seemed to me desirable that further evidence should be afforded of the effect of mere occlusion from air in maintaining the blood fluid. If the ammonia theory were true, then if blood could be shed directly from a living vessel into an air-tight receptacle composed of ordinary matter it ought to remain fluid. For this purpose, I made the following experiment:—I tied into the jugular vein, V (Fig. 1), of a sheep a long vulcanized india-rubber tube, T, adapted by means of short pieces of glass tube at its extremities, both ends being connected with the vessel so that the current of blood might be permitted to flow through the tube, and then continue its natural course. When it had been ascertained that the blood was circulating freely through the tube, which could be readily done by placing the finger on the cardiac aspect of the vein, which was then made to swell if the circulation was proceeding through the tube, pieces of string well waxed were tied at intervals of about two inches round the tube, which was thus converted into a number of air-tight receptacles containing blood, which certainly had no opportunity for the escape of ammonia. The tube was then removed, and I found, in accordance with the view which I was then disposed to entertain, that the blood, instead of coagulating completely in a few minutes as it would have done if shed into a cup, remained partially fluid in these receptacles after the lapse of three hours. But I have since found that if the experiment be repeated in the same way as regards its earlier stages, and if, after a few of the strings have been tied on, the tube be cut across, the blood which is in the part of the tube in the vicinity of the air, just like that which is in the air-tight receptacles, remains fluid in part for two or three hours. In short, that my precautions in ensuring that these receptacles should be air-tight were, in so far as they applied to that object, utterly unnecessary. I mention this partly as an illustration of the deceptions to which one is liable in this inquiry, and partly because the experiment thus modified seems to tell as clearly against

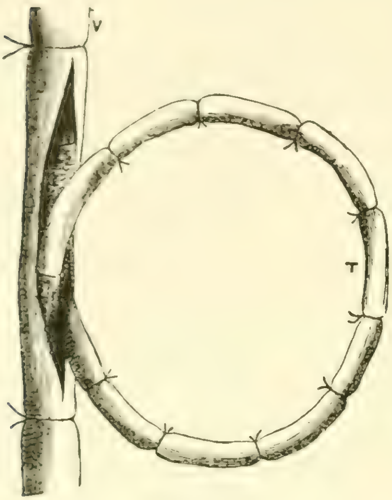


Fig. 1.

the ammonia theory as the original one seemed to tell in favour of it. Those receptacles which had been formed by the application of ligatures before the tube was opened afforded certainly no opportunity for the escape of ammonia, and yet in them the blood coagulated as quickly as in those which had communication with the air—implying that facility for the evolution of ammonia does not in itself affect the process of coagulation at all.

How then, it may be said, is the persistent fluidity of the blood under these circumstances to be explained? That will become more obvious than I can make it at present in the sequel, but in the meantime I may observe that there are probably two explanations: one is, the coolness of the tube, and the other, far more important, that the blood, in slipping through this cylindrical tube, had had little opportunity of being influenced by its walls. The portion of the blood that came first in contact with the walls of the tube had coagulated; and it is to be observed that I never found, in these experiments, the blood altogether fluid, even after a comparatively short time: there has always been a certain amount of coagulation, and only a certain amount of fluidity. A layer of blood having thus coagulated upon the internal surface of the tube, the fresh blood, which continued to flow through it, was not brought into contact with the walls of the tube at all, but with their lining of coagulated blood.

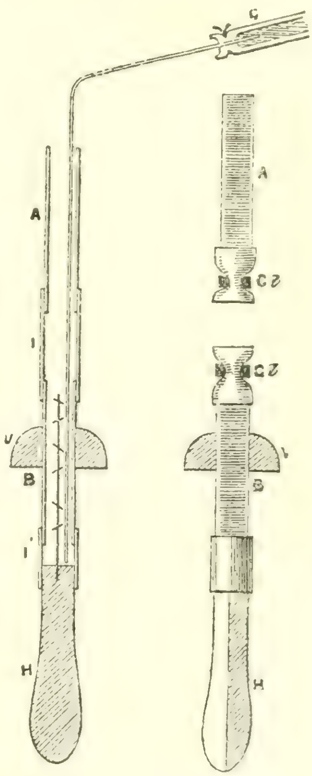


FIG. 2.

It has been long known that if blood is stirred with a rod, the process of coagulation is promoted. It seemed desirable to ascertain distinctly whether the cause of this was the contact of the foreign solid, or the opportunity given for the escape of ammonia; for it is quite true that, in the ordinary process of stirring blood, more or less air is mixed with it. For the purpose of determining this I devised a somewhat complicated experiment, which, however, it may be worth while to mention. I made an apparatus (Fig. 2) of two portions of glass tube, A and B, connected in a vertical position by means of vulcanized india-rubber, I, the lower portion of the glass tube being also connected by india-rubber, I′, with a wooden handle, which handle, H, was provided with an upright piece of wire, from which spokes projected in different directions, so that they would, when moved, act as a churn on any blood contained in the lower portion of tube. When the lower piece of tube was fixed by mean of a vice, V, the flexibility of the india-rubber permitted the churn to be rotated so as to expose the blood to its influence. This having been arranged, I first poured in strong liquor ammoniae, so as to get rid of any slight acidity which the constituents of the apparatus might be conceived to possess, and then, having poured out the ammonia, filled up the apparatus with water, and boiled the whole in a large glass test-tube till all bubbles of air, in any portion of it, were expelled. Having then tied into a branch of the carotid artery, C, of a calf a bent tube of small diameter, as represented, and having permitted the blood to flow till it escaped at the orifice of the tube, I compressed the artery and passed the tube down through the water to the bottom of the apparatus, and then let the blood flow again, which had the effect of displacing all the water ; and when the blood appeared at the top of the apparatus, the tube was withdrawn, when two effectual clamps, Cl, Cl, were placed on the vulcanized india-rubber connecting A and B ; the india-rubber was then divided between the clamps, and we had the state of things represented at the right-hand side of the diagram. The upper portion of the apparatus, the orifice of which was exposed to the air, was set aside and left undisturbed. Having ascertained that the lower portion had been effectually sealed by the clamp, and thus prevented from any opportunity of escape of ammonia, I subjected it to the action of the churn for a certain number of minutes. It so happened that the blood of that calf was very slow in coagulating. I knew this from previous experiments on the animal, and therefore continued the action of the churn for a considerable time, viz. thirty-seven minutes. I then found the wire enveloped in a mass of clot ; and examination of the fluid residue with a needle indicated that the fibrine had been all withdrawn from the blood on which the churn had acted. I did not now examine the other portion of the apparatus, which had been set aside, but at the end of an hour and a quarter, when more than double the time had elapsed, I investigated this, and found the blood in it, for the most part, still fluid and coagulable. Thus the blood in the churn, which, from the time it left the artery, had no opportunity of parting with its ammonia, coagulated much more rapidly than that in an open vessel. The difference between the two was that the lower portion of the blood had been freely exposed to the influence of the foreign solid, whereas the other had only been subjected to the action of the wall of the tube.

The same principle may be illustrated by an exceedingly simple experiment which I performed only this very day. Receiving blood from the throat of a bullock into two similar wide-mouthed bottles, I immediately stirred one of them with a clean ivory rod for ten seconds very gently, so as to avoid the introduction of any air, and then left both undisturbed. At the end of a certain number of minutes I found that, while the blood which had not been disturbed could be poured out as a fluid, with the exception of a thin layer of clot on the surface, and an incrustation on the interior of the vessel, the blood in the other vessel, which had been stirred for so brief a period, was already a solid mass.

I have only lately been aware of the great influence exerted upon the blood by exposure for a very short time to a foreign solid, and I feel that many of my own experiments, and many performed by others, have been vitiated for want of this knowledge. Take, for example, the effect of a vacuum, which was observed by Sir Charles Scudamore to promote coagulation. This has been considered by Dr. Richardson as an illustration of his theory, the vacuum being supposed to act by favouring the escape of ammonia. I have lately inquired into this subject, and I feel no doubt whatever that the greater rapidity of coagulation in a vacuum depends simply on the greater disturbance of the fluid. I made the following experiment :—I filled three bottles, such as these, from the throat of a bullock, placed one of them under the small bell jar of an air-pump in good order and exhausted it, leaving the other two undisturbed. The blood happened to be slow in coagulating, and at the end of about forty minutes, in the vessels where the blood had been undisturbed, there was only a slight film of coagulum on the surface, whereas the blood under the vacuum was found on examination to have a very thick crust of clot upon it. But during the process of exhaustion the blood had bubbled very much. Indeed, any exhaustion of blood recently drawn which is sufficient to cause the evolution of its gases induces great bubbling, so that the pump cannot be used freely for fear of the froth overflowing. To this disturbance, involving the exposure of successive portions of blood in the bubbles to the sides of the vessel, I was inclined to attribute the more rapid coagulation ; but in order to prove the point, I stirred for a few seconds the blood in one of the vessels hitherto undisturbed. After eight minutes I emptied the three vessels. I found that that blood which had not been disturbed at all, either by the vacuum or by the rod, was still almost entirely fluid, only showing a thin crust upon the glass and on the surface exposed to the air. The blood which had been subjected to the vacuum had a thick crust of clot on the surface, and the sides of the glass were also thickly encrusted, but it still contained a considerable quantity of fluid that could be poured out from its interior. But that blood which had been stirred for only a few seconds was a solid mass throughout. In other words, gentle stirring of the blood for a few seconds had much greater effect in producing coagulation than the protracted and efficient exhaustion which was continued for upwards of forty minutes, which was a considerable time after all evolution of gas, as indicated by bubbles, had ceased.

Other experiments precisely similar in their effect were performed. I therefore feel no hesitation in stating that the effects of a vacuum, regarding which, indeed, the statements of different experimenters have hitherto been conflicting, afford no evidence in favour of the ammonia theory.

There is another point of very great interest in the history of the coagulation of the blood, which has been supposed to give support to the ammonia theory; and that is, the effect of temperature. It has been long known that blood coagulates more rapidly at a high than at a low temperature, and, indeed, a little above the freezing-point remains entirely fluid. This seemed beautifully in harmony with the ammonia theory, as heat would naturally promote, and cold retard the evolution of the alkali, and a depression of temperature to near the freezing-point might be reasonably supposed to prevent its escape altogether. Indeed, Dr. Richardson mentions as a fact, that ammonia artificially mixed with blood ceases to be given off under such circumstances.

Though thinking it not unlikely that this was the true explanation of the influence of temperature on coagulation, I thought it worth while to subject the matter to experiment. For that purpose I kept the blood of a horse fluid by means of a freezing mixture, and afterwards by ice-cold water; and when the corpuscles had subsided from the upper part of the blood, I cautiously added to the liquor sanguinis extremely dilute ice-cold acetic acid till it was of distinctly acid reaction, the liquor sanguinis being of a colour that permitted the delicate application of test-paper, which is impossible with red blood. By this means any free ammonia which the fluid might have contained must have been neutralized, yet so long as it was kept in the cold it continued fluid, but when brought into a warm room coagulated just as a specimen which had not been acidulated. Thus, when there could be no free ammonia in the liquor sanguinis at all, it was still affected as usual by temperature.

This experiment may not be satisfactory to all minds, though I confess it appears so to me; and, as this is a point of very great interest, I have sought in another way for evidence regarding it. First, however, I will mention an experiment which will not at once appear to bear on the question of temperature. I drew out a fine glass tube in such a way as to produce a fusiform receptacle continued longitudinally each way into a tube of almost capillary fineness for about two inches, which again expanded at the end, as represented in Fig. 3. Having squeezed out a drop of blood from my finger, I sucked up a portion into the tube till the receptacle A and its capillary extensions were filled. I then broke off the expanded ends, and placed the little tube thus filled, B, in a bath of the strongest liquor ammoniae. Here certainly the blood was in circumstances in which it could not lose ammonia, but where any change in its amount must be by way of increase, and yet I found, on opening the receptacle by snapping it across after a scratch with a file, that instead of remaining longer fluid than in a watch-glass, the blood in it, being more in contact with the glass, was always more quickly coagulated, while coagulation was still more rapid in the capillary tube, where the blood was still more exposed to the influence of the foreign solid—the greater proximity to the liquor ammoniae having no influence upon it.

It may perhaps be argued that the drop of blood employed being a small drop, and this small drop having been drawn up by suction into the tube, it might have parted with its ammonia before it got into the tube ; but then (and now comes the bearing of the experiment on the effect of temperature) I found, if I placed a similar tube filled in the same way in a vessel of snow,

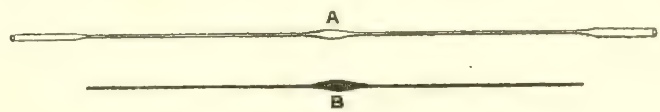


Fig. 3.

so as not to freeze it but to keep it ice-cold, the blood in it remained fluid as long as I chose to keep it there. Now if all the ammonia had left the blood before it was introduced into the tube, cold ought, according to the ammonia theory, to have had no effect in retarding its coagulation ; for, according to that theory, cold operates by retaining the ammonia. On the other hand, if we take the other alternative and suppose that any ammonia which the blood might have contained was still in these tubes, the former experiment proves clearly that the retention of ammonia has no effect in producing fluidity—no effect in preventing coagulation ; and if the retention of ammonia has no effect in preventing coagulation, then cold certainly cannot prevent coagulation by retaining the ammonia, because, even if retained, it would not influence the result. In whatever way we look at them, therefore, these simple experiments prove conclusively that cold maintains the fluidity of the blood in some manner unconnected with any influence it may exert upon ammonia.

Then, again, I varied the experiment in this way. I placed such little tubes of blood in baths of liquor ammoniae at different temperatures. By careful management, guarding against the volatilization of ammonia and consequent reduction of temperature, I succeeded in employing satisfactorily a bath of liquor ammoniae at 100° Fahr., the blood being in the bath within a few seconds of its leaving the vessels of my finger, and I found that the high temperature, though under such circumstances it could not possibly dissipate any ammonia from the blood, yet accelerated its coagulation in precisely the same way as when it was applied to blood in watch-glasses exposed to the air.

It is clear, then, that the promotion of the solidification of fibrine by heat is as independent of the evolution of ammonia as the coagulation of albumen under the same agency. Indeed, it seems probable that the two cases are analogous, except that a higher temperature is required in the one than in the other.

When fine tubes containing blood were placed in liquor ammoniae, the alkali acted only upon those parts which were close to the ends of the tubes ; a very small portion was rendered brown by it, and beyond that a little was kept permanently fluid, but the chief length of the blood in the tube was unaffected. Having thus ascertained that ammonia travels so slowly along tubes of this capillary fineness, I thought I might have an opportunity of giving the ammonia theory a fair test by tying such a tube as has been above described into the jugular vein of a rabbit and filling it directly from the vessel, and then ascertaining whether there was any evidence of retardation of coagulation in the blood thus imprisoned. But I could discover no such evidence, although I sought for it in confirmation of a view I then held. To this, however, there is one special exception to be made, viz. in the case of asphyxia. I found that if two such tubes were filled from the same blood-vessel of a creature, one under normal circumstances, and the other after asphyxia had been induced, there was a most remarkable difference between the rates of coagulation of the blood in the two tubes, the asphyxial blood coagulating very much more slowly than the ordinary blood ; but when the asphyxial blood was shed into a watch-glass and air was blown through it, it coagulated rapidly, showing that in the state of asphyxia there must be some volatile element in the blood which has an effect in retarding coagulation.

Supposing at first that this volatile element must be ammonia, I hoped to be able by chemical means to find evidence of its accumulation in asphyxia, and thus add a fact of great interest to physiology. Imitating experiments previously made by Dr. Richardson, I passed air successively through blood and through hydrochloric acid, and then estimated the amount of ammonia acquired by the latter by means of bichloride of platinum. In order to prevent the possibility of the loss of any ammonia, I directed blood from the carotid artery of a calf fairly into a Wolfe's bottle by means of a vulcanized india-rubber tube tied into the vessel, and then drew a certain volume of air through it by means of an aspirating jar, the experiment being performed first before, and then during asphyxia. The same procedure was adopted with a second calf, the animal being in each case under chloroform, which does not interfere with the development during asphyxia of the peculiarity in the blood above alluded to, but I could not find satisfactory evidence of accumulation of ammonia; and without going further into the question at present, I may say that it seems much more probable that the effect is due to carbonic acid, which is known to have a retarding influence on coagulation, and which probably accumulates greatly in asphyxial blood.

But in justice to the author of the ammonia theory, and to myself, too, who at one time expressed a qualified belief in it, it is but fair to say that this theory is extremely plausible. It has been well shown by Dr. Richardson that ammonia is a substance well fitted to keep the blood fluid if it be present in a sufficient quantity. An experiment of my own illustrates very well the same point. I drew out a tube about a quarter of an inch in calibre (Fig. 4), so that

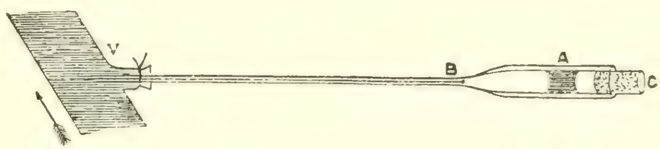


FIG. 4

while for two inches at one end it retained its original width, the rest (some ten inches) was pretty narrow, though far from having the capillary fineness of those before described. Into the thick part I introduced a drop of strong liquor ammoniae, A, and then securely corked that end of the tube, C. The object of this was that there should be a strong ammoniacal atmosphere in the narrow part of the tube. I then opened a branch of a vein, V, in the neck of a sheep, introduced the narrow end of the tube into the vessel, and pushing it in so that its orifice should be in the current of the main trunk of the vein, tied it in securely. I then removed the cork and made pressure on the vein at the cardiac side, causing the vessel to swell and blood to pass into the fine part of the tube, and before the blood had reached the part of the glass moistened by the ammonia I put in the cork again and withdrew the tube. In a short time, on introducing a hook of fine wire into the extremity of the tube, I found the blood already coagulated, but on filing off a small portion of the tube I found the blood there fluid. The portion of blood thus exposed soon coagulated, when, a second small piece of the tube being removed by the file, fluid blood was again disclosed, which again soon coagulated; and this proceeding was repeated with the same results time after time, till, near the thick part of the tube, the ammonia in the blood was so strong as to prevent coagulation altogether.

This experiment illustrates how fitted the ammonia is to maintain the fluidity of blood, and also how apt it is, when present in the blood, to fly speedily off from it, leaving it unimpaired in its coagulating properties ; and it must be confessed that the end of the tube sealed with a small clot resembled most deceptively the extremity of a divided artery similarly closed. But although the experiment seems in so far to favour the ammonia theory, it will tell differently when I mention the object with which it was performed. It appeared to me that, if the cause of the fluidity of the blood was free ammonia, then, if I provided an ammoniacal atmosphere in the tube, and introduced blood by pressure directly from the vein into this ammoniacal atmosphere, this blood, lying between the strong ammoniacal atmosphere on the one side and the ammonia naturally present in the blood within the vein on the other side, ought to remain fluid ; and if it did remain fluid, this would tend to confirm the ammonia theory by making it appear that the volatile material was the same at both ends of the tube. But, to my disappointment, I invariably found that if I drew away the tube after a few minutes only had elapsed, there was already a clot in its extremity ; in other words, the ammonia had diffused from the end of the tube into the blood within the vein as into a non-ammoniacal atmosphere. This experiment alone, if duly considered, would, I think, suffice to show that the blood does not contain enough ammonia to account for its fluidity.

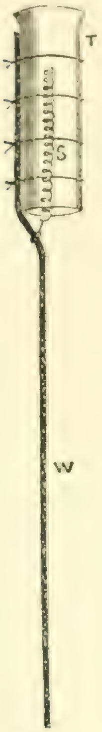


Fig. 5.

One more experiment, however, may be adduced with the same object. I mounted a short but wide glass tube, open at both ends (T, Fig. 5), upon the end of a piece of strong wire, W, and connected with the latter a coil of fine silver wire, S, so that it hung freely in the tube. I then opened the carotid artery of a horse, and through the wound instantly thrust in the apparatus so far that I was sure the tube lay in the common carotid, which in veterinary language means the enormous trunk common to both sides of the neck of the animal. The tube being open at both ends, and slightly funnel-shaped at that end which was directed towards the heart, had thus a full current of arterial blood streaming through it. Having ascertained how long the arterial blood took to show the first appearance of coagulation in a watch-glass, I very soon after removed the apparatus, and, on taking out the coil of silver wire, found that it was already crusted over with coagulum. Yet here assuredly there had been no opportunity for the escape of ammonia.

From this experiment it is obvious that there is a very great difference between ordinary solid matter and the living vessels in their relation to the blood. But the same conclusion may be drawn much more simply from experiments which I had the opportunity of performing after making an observation which it seems strange should have been left for me to make, and which, I may say, was made by myself purely accidentally ; and this is, that the blood of mammalia, although it coagulates soon after death in the heart and the principal arterial and venous trunks, remains fluid for an indefinite period in the small vessels. If, therefore, a ligature be tied round the foot of a living sheep a little below the joint which is divided by the butcher, the foot being removed and taken home with the blood retained in the veins by the ligature, we have a ready opportunity of investigating the subject of coagulation, and of making observations as satisfactory as they are simple. Here are two feet provided in the way I have alluded to. A superficial vein in each foot has been exposed. The veins I see have contracted very much since I reflected the skin from them before our meeting ; and I may remark that such contraction, dependent on muscular action, may occur days after amputation, indicating the persistence of vital properties in the veins. Now as I cut across this vein, blood flows out, fluid but coagulable. Into the vein of this other foot has been introduced a piece of fine silver wire, and when I slit up the vein you will see the effect it has produced. Exactly as far as the silver wire extends, so far is there a clot in this vessel. Now this experiment, very simple as it is, is of itself sufficient to prove the vital theory in the sense that the living vessels differ entirely from ordinary solids in their relation to the blood. It is perfectly clear that by introducing a clean piece of silver wire (and platinum or glass or any other substance chemically inert would have had the same effect) I do not add any chemical material or facilitate the escape of any, and yet coagulation occurs round about the foreign solid.

Again, if a blood-vessel be injured at any part, coagulation will occur at the seat of injury. As a good illustration of this, and also as bearing upon the ammonia theory, I may mention the following experiment. Having squeezed the blood out of a limited portion of one of the veins of a sheep's foot, and prevented its return by appropriate means, I treated the empty portion with caustic ammonia, the neighbouring parts of the vein being protected from the irritating vapour by lint steeped in olive oil. After the smell of ammonia had passed off, I let the blood flow back again and left it undisturbed for a while, when I found on examination a cylindrical clot in the part that had been treated with ammonia, while in the adjacent parts of the same vessel the blood remained fluid. I repeated this experiment several times and always with the same result. Where the ammonia had acted there was a clot. The chemical agent used here was one which, so long as any of it remained, would keep the blood fluid, yet its ultimate effect was to induce coagulation, the vital properties of the vein having been destroyed by it.

If a needle or a piece of silver wire is introduced for a short time into one of the veins of the sheep's foot, it is found on withdrawal to be covered over with a very thin crust of fibrine, whereas the wall of the vessel itself is never found to have fibrine or coagulum adhering to it unless it has been injured. Now this seems to imply that the ordinary solid is the active agent with reference to coagulation—that it is not that the blood is maintained fluid by any action of the living vessels, but that it is induced to coagulate by an attractive agency on the part of the foreign solid. We see at any rate that the foreign solid has an attraction for fibrine which the wall of the vessel has not.

And yet I own I was at first inclined to think that the blood-vessels must in some way actively prevent coagulation. There were two considerations that led to this view. One was, that the blood remained fluid in the small vessels after death, but coagulated in the large. Now why should that be ? It seemed only susceptible of explanation from there being some connexion between the size of the vessel and the circumstance of coagulation. It looked as if in the small veins the action of the wall of the vessel was able to control the blood and keep it fluid, but that the large mass in the principal trunks could not be so kept under control. The other circumstance was the rapid coagulation of a large quantity of blood shed into a basin. Why should this occur unless there was some spontaneous tendency in the blood to coagulate ? It seemed scarcely credible that it was the result of contact with the surface of the basin.

Both these notions, however, have since been swept away. In the first place, I have observed recently that it is by no means only in small vessels that the blood remains fluid after death. If blood be retained within the jugular vein of a horse or ox by the application of ligatures, either before or after the animal has been struck with the pole-axe, it will often continue fluid, but coagulable, in that vessel, which is upwards of an inch in diameter, for twenty-four or even forty-eight hours after it has been removed from the body. I say often, but not always. The jugular vein seems to be in that intermediate condition, between the heart and the small vessels, in which it is uncertain whether it will retain its vital properties for many hours, or will lose them in the course of one hour or so. Unfortunately for my present purpose, it happens that in this jugular vein, removed from an ox six hours ago, coagulation has already commenced, as I can ascertain by squeezing the vessels between my fingers. But now that I lay open the vessel, you observe that the chief mass of its contained blood is still fluid, and we shall at all events have an opportunity of seeing that what is now fluid will in a short time be coagulated. It is an interesting circumstance with reference to the question which we are now considering, that the coagulation always begins in contact with the vein, indicating that it is not the wall of the vessel that keeps the blood fluid, but that, on the contrary, the wall of the vessel, when deprived of vital properties, makes the blood coagulate.

The observation of the persistent fluidity of the blood in these large vessels furnished the opportunity of making a very satisfactory experiment, which I hoped to have exhibited before the Society, but as there was some clot in the vein I did not think fit to run the risk of failure. The experiment is performed in the following way. A piece of steel wire is wound spirally round one of the veins in its turgid condition, and with a needle and thread the coats of the vessel are stitched here and there to the wire, care being taken to avoid puncturing the lining membrane, and thus the vessel is converted into a rigid cup. Two such cups being prepared, and the lining membrane of the vein being everted at the orifice of each so as to avoid contact of the blood with any injured tissue, I found that, after pouring blood to and fro through the air in a small stream from one venous receptacle into the other half a dozen times, and closing the orifice of the receptacle to prevent drying, the blood was still more or less completely fluid after the lapse of eight or ten hours. On the other hand, if a fine sewing needle is pushed through the wall of an unopened vessel so that its end may lie in the blood, it is found on examination, after a certain time has elapsed that the needle is surrounded with an encrusting clot. It is scarcely necessary to point out how entirely the ammonia theory and the oxygen theory, as well as that of rest, fail to account for facts like these.

While the blood may remain fluid for forty-eight hours in the jugular vein of a horse or an ox, it coagulates soon after death in the heart of very small animals, such as mice, so that it is obvious that the continuance of fluidity in small vessels is not due to their small size.

It is a very curious question, What is the cause of the blood remaining so much longer fluid in some vessels than in others? I believe that we must accept it simply as an ultimate fact, that just as the brain loses its vital properties earlier than the ganglia of the heart, so the heart and principal vascular trunks lose theirs sooner than the smaller vessels of the viscera, or than more superficial vessels, be they large or small. We can see a final cause for this, so to speak. So long as the heart is acting, circulation will be sure to go on in the heart and principal trunks; whereas, on the contrary, the more superficial parts are liable to temporary causes of stagnation, and occasionally to what amounts to practical severance from vascular and nervous connexion with the rest of the body; and it is, so to speak, of great importance that the blood should not coagulate so speedily in the vessels of a limb thus circumstanced as it does in the heart after it has ceased to beat. Were it not for this provision, the surgeon would be unable to apply a tourniquet without fear of coagulation occurring in the vessels of the limb. As an illustration of the importance of a knowledge of these facts, I may mention a case that once occurred in my own practice. I was asked by a surgeon in a country district to amputate an arm which he despaired of. The brachial artery had been wounded, as well as veins and nerves, and at last, being foiled with the haemorrhage, he wound a long bandage round the limb at the seat of the wound as tightly as he possibly could. It had been in this condition with the bandage thus applied for forty-eight hours when I reached the patient, and the limb had all the appearance of being dead. It was perfectly cold, and any colour which it had was of a livid tint. But having been lately engaged in some of the experiments which I have been describing, and having thus become much impressed with the persistent vitality of the tissues and the concomitant fluidity of the blood, I determined to give the limb a chance by tying the brachial artery. Before I left the patient's house he had already a pulse at the wrist, and I afterwards had the satisfaction of hearing that the arm had proved a useful one.[1]

One of the two arguments in favour of activity on the part of the vessels as a cause of the fluidity of the blood having been completely disposed of, let us now consider the other, viz. the rapid coagulation of blood shed into a basin, appearing at first sight to imply a spontaneous tendency of the blood to coagulate, such as would have to be counteracted by the vessels. This also has proved fallacious.

In the first place it appears that the coagulation, after all, does not go on in a basin so suddenly as one would at first sight suppose, but always commences in contact with the foreign solid. When blood has been shed into a glass jar, if, on the first appearance of a film at the surface, you introduce a mounted needle curved at the end between the blood and the side of the glass and make a slight rotatory movement of the handle, you see through the glass the point of the needle detaching a layer of clot whatever part you may examine. The process of coagulation having thus commenced in contact with the surface of the vessel into which the blood is shed, may, under favourable circumstances, be ascertained to travel inwards, like advancing crystallization, towards the centre of the mass. It appears, however, that this extension of the coagulating

[1] See above, p. 85.

process would not take place had not the blood been prepared for the change by contact, during the process of shedding, with the injured orifice of the blood-vessel and with the surface of the receptacle. I have only very recently become acquainted with the remarkable subtlety of the influence exerted upon blood by ordinary solids. I was long since struck with the fact that if I introduced the point of an ordinary sewing needle through the wall of a vein in a sheep's foot and left it for twelve hours undisturbed, the clot was still confined to a crust round the point of the needle, implying that coagulum has only a very limited power of extension. I thought, therefore, that by proper management it might be possible to keep blood fluid in a vessel of ordinary solid matter lined with clot. But various attempts made with this object failed entirely, till I lately adopted the following expedient. Having opened the distal end of an ox's jugular vein containing blood and held in the vertical position, taking care to avoid contact of any of the blood with the wounded edge of the vessel, I slipped steadily down into it a cylindrical tube of thin glass, somewhat smaller in diameter than the vein, open at both ends, and with the lower edge ground smooth in order that it might pass readily over the lining membrane, and so disturb the blood as little as possible by its introduction, and influence only the circumferential parts of its contents. The tube was then kept pressed down vertically upon the bottom of the vein by a weight, in a room as free as possible from vibration, and I found on examining it at the end of twelve hours that the clot was a tubular one, consisting of a crust about one-eighth of an inch thick next the glass and the part exposed to the air, but containing in its interior fluid and rapidly coagulable blood. In another such experiment, continued for twenty-four hours, though the crust of clot was thicker, the central part still furnished coagulable blood.

But it may perhaps be argued by those who say that the blood-vessels are active in maintaining fluidity that the small portion of the vein covering the end of the tube was acting upon the blood, which certainly was fluid where in contact with it, the clot being in the form of a tube open at the lower end. To guard against such an objection I made the following experiment :—I extended a tube like that above described by means of thin sheet gutta-percha, G (Fig. 6 *a*), contriving that the internal surface of the gutta-percha should be perfectly continuous with that of the glass tube as represented in section in Fig. 6 *b*. The lower part of the gutta-percha tissue was strengthened by a ring of soft flexible wire such as is used by veterinary surgeons for sutures, and the wire, W, was also extended upwards to the top of the glass so as to maintain the rigidity of the gutta-percha portion during its introduction into a vein, but at the same time, from its softness, permit the gutta-percha part to be bent at a right angle after it had been introduced, and so close the orifice of the glass tube with ordinary solid matter. In Fig. 6 *c* the tube is represented pressed down by a weight in a vein, V, with blood, B, in the glass portion, while the gutta-percha part closes it below. At the same time I performed a comparative experiment, to which I would invite particular attention, although I am sorry at this late hour to occupy the attention of the Society so long. I tied a thin piece of gutta-percha tissue over the lower end of a similar glass tube, and simply poured blood into it from the jugular vein of an ox. I wished to compare the condition of blood which had been simply poured into a tube, with blood which had been introduced without any disturbance of its central parts. But in order to make the

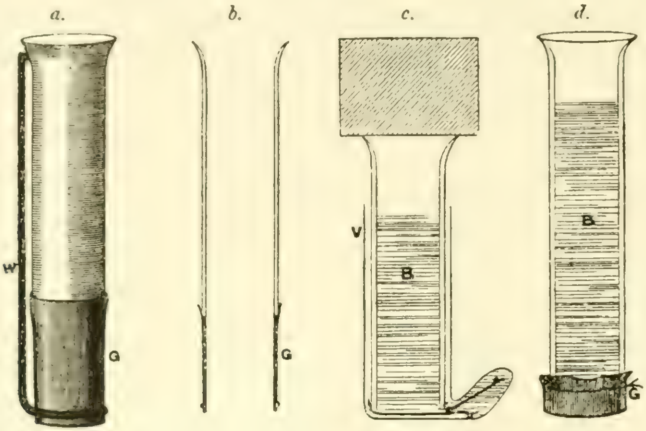


Fig. 6.

experiment a fair one, as it might be said that the blood poured from the vein had been more exposed to the air than that into which the tube was slipped, I proceeded in the following way: I obtained a long vein containing plenty of blood, and having first filled the second tube, with the gutta-percha bottom (Fig. 6 *d*), by simply pouring blood into it from the vein, I cut off a portion of the vein which had been thus emptied, and having tied one end and everted the lining membrane of the other end, and having also everted the lining membrane of the orifice of the remainder of the vessel which was full, I poured the blood from the full portion through the air into the empty part. In doing this I had difficulty in getting blood enough, and it passed through the air in slow drops, and that only when the vein was squeezed by my warm hand. At last, having introduced sufficient for the purpose, I slipped down the compound tube and bent its gutta-percha portion, as represented in Fig. 6 *c*, and left both tubes for a while undisturbed. At the end of three hours and a half I found that the blood which had been simply poured in was a mass of clot, and fluid squeezed from it yielded no threads of fibrine, coagulation being complete. How long it had been so I do not know. I did not examine the other blood until seven hours and three quarters had expired, and then found that, just as in the cases where a simple glass tube was introduced, the clot was tubular, and the chief part of the blood was still fluid in its interior, the only difference being that in this case the clot formed a complete capsule, being continued over the gutta-percha instead of being deficient below, as it was when the vein closed the end of the tube. Now if we consider the two parts of this comparative experiment, we see that the receptacles in which the blood was ultimately contained were precisely similar in the two cases, viz. glass tubes closed below with gutta-percha; and that the blood which was simply poured into the tube was much less exposed to the air than the other, and also was not subjected, like it, to elevation of temperature, a circumstance which promotes coagulation; but yet this blood became completely coagulated in a comparatively short time, whereas the other after a much longer time was coagulated only in a layer in contact with the foreign solid. But in the latter case the blood had been so introduced as to avoid direct action of ordinary matter on any but the circumferential parts of it, whereas in the former, though poured quickly, it had run down the side of the glass, and as a consequence of this almost momentary contact with the foreign solid, the central parts, like the circumferential, underwent the process of coagulation.

Mysterious as this subtle agency of ordinary solids must appear, its occurrence is thus matter of experimental demonstration, and by it the coagulation of blood shed into a basin is accounted for; while it is also shown conclusively from this experiment that the blood, as it exists within the vessels, has no spontaneous tendency to coagulate, and therefore that the notion of any action on the part of the blood-vessels to prevent coagulation is entirely out of the question. The peculiarity of the living vessels consists not in any such action upon the blood, but in the circumstance, remarkable indeed as it is, that their lining membrane, when in a state of health, is entirely negative in its relation to coagulation, and fails to cause that molecular disturbance or, if we may so speak, catalytic action which is produced upon the blood by all ordinary matter.

I afterwards found that the simplest method of maintaining blood fluid in a vessel composed entirely of ordinary matter was to employ a glass tube similar to those above described, except that its upper end was closed by a cork perforated by a narrow tube terminating in a piece of vulcanized india-rubber tubing that could be closed by a clamp. This tube was slipped down into a vein till the blood, having filled it completely, showed itself at the orifice of the india-rubber tubing, to which the clamp was then applied. The whole apparatus was now quickly inverted, and the vein was drawn off from over the mouth of the tube, which was then covered with gutta-percha tissue to prevent evaporation. After the inverted tube had been kept undisturbed in the vertical position for nineteen hours and three-quarters coagulable blood was obtained from the interior of the clot.

We have seen that a clot has but very slight tendency to induce coagulation in its vicinity unless the blood has been acted on by an ordinary solid, and it is probable that with perfectly healthy blood it would be unable to produce such an effect at all. This appears to me to be very interesting physiologically, but especially so with reference to pathology. I must not go now fully into the circumstances that lead me to it, but I may express the opinion I have formed, that clot must be regarded as living tissue in its relation to the blood. It is no doubt a very peculiar form of tissue, in this respect—that it is soft, easily lacerable, and easily impaired in its vital properties. If disturbed, as in an aneurysm, it will readily be brought into that condition which leads to the deposition of more clot ; but if undisturbed, it not only fails to induce further coagulation, but seems to undergo spontaneous organization. I have seen a clot in the right side of the heart, and extending into the pulmonary artery and its branches, unconnected with the lining membrane of auricle or ventricle or with the pulmonary artery except at one small spot where it had a slight adhesion, developed into perfect fibrous tissue by virtue, it would appear, of its own inherent properties. Another observation which I once made, and which then completely puzzled me, now seems capable of explanation. In laying open the blood-vessels of a dead body I observed in many of the veins a delicate white lace-like tissue which evidently must have been formed from a clot. This I now believe to have had the same relation to the coagulum as the flimsy cellular tissue of old adhesions has to lymph.

It may not be altogether superfluous to mention some other facts illustrative of the active influence of ordinary matter in promoting coagulation, and the negative character of the lining membrane of the vessels. I find that a needle introduced into one of the veins of the foot of a sheep for a much shorter time than is necessary to produce the first appearance of the actual deposit of fibrine upon it, leads after a while to coagulation where the needle had lain ; in other words, that a foreign solid, by a short period of action on the blood, brings about a change that results in coagulation, though the blood still lies in the living vessels. I have also ascertained that after blood has been made to coagulate in a particular vessel by introducing a needle into it, if the coagulum as well as needle is removed, and more fluid blood is allowed to pass in, this blood remains fluid for an indefinite period, showing that the needle had not impaired the properties of the vessel by its presence ; so that the previous coagulation must be attributed not to any loss of power in the vein but simply to the action of the foreign solid.

In seeking for an analogy to this remarkable effect of ordinary solids upon the blood, we are naturally led to the beautiful observations of Professor Graham, lately published in the *Philosophical Transactions.* He has there shown what insignificant causes are often sufficient to induce a change from the fluid or soluble to the 'pectous' or insoluble condition of 'colloidal' forms of matter. Indeed, Mr. Graham has himself alluded to the coagulation of fibrine as being probably an example of such a transition.

There is, however, another remarkable circumstance that must be taken into consideration, of which I myself have been only recently aware, and which may be new to several Fellows of the Society ; and that is, that in spite of the influence of an ordinary solid the liquor sanguinis is not capable of coagulating *per se.* It was observed many years ago by my colleague, Professor Andrew Buchanan, of Glasgow, that the fluid of a hydrocele, generally regarded as mere serum, coagulated firmly if a little coagulum of blood diffused in water was added to it—an effect which he was disposed to attribute to the agency of the white corpuscles.[1] I repeated Dr. Andrew Buchanan's observations last year, and satisfied myself first that the diffused clot did not act simply by providing solid particles to serve as starting-points for the coagulating process. I tried various different materials in a finely divided state, and found that none of them, except blood, produced the slightest effect. But I found that if a mixture of serum and red corpuscles from a clot was added to some of this hydrocele-fluid, it was soon converted into a firm solid mass. If a small quantity of the serum and corpuscles was dropped into the fluid and allowed to subside without stirring, coagulation rapidly took place in those parts where the red corpuscles lay, while other parts of the fluid remained for a long time uncoagulated. This seemed to indicate that the red corpuscles had a special virtue in inducing the change. I confess, however, that till very lately I was inclined to suppose that in the hydrocele-fluid the fibrine must be in some peculiar spurious form. We know that the buffy coat of the horse's blood coagulates in a glass without addition of clot, and we know that lymph coagulates, so that I did not doubt that liquor sanguinis would always undergo the change when influenced by ordinary matter. But an observation which I made not many days ago shows that this was a mistake. I obtained the jugular vein of a horse, and having kept it for a while in a vertical position till I could see through its transparent coats that the red corpuscles had fallen from the upper part, I removed all

[1] *Proceedings of the Glasgow Philosophical Society*, February 19, 1845.

bloody tissue from that part of the vein, and punctured it so as to let out the liquor sanguinis into a glass. Finding after eighteen minutes that the liquid had not begun to coagulate, I added a drop of serum and corpuscles to a portion of it, and within seven minutes there was a clot wherever the corpuscles lay, whereas the rest of the fluid was still very imperfectly coagulated after another half-hour had elapsed. That the liquor sanguinis to which no addition had been made coagulated at all was sufficiently explained by microscopic investigation, which showed not only abundant white corpuscles, but also several isolated red ones that had not subsided. This observation was made three hours after the death of the horse, but I obtained essentially similar results on repeating the experiment in another horse an hour after death; so that there can be no doubt whatever that the fibrine was in the same condition as it is in the blood-vessels of a living animal. The observation appears also particularly satisfactory on this account, that the liquor sanguinis was not separated from the corpuscles by any process of transudation through the walls of the blood-vessels, which might be conceived to involve retention of some constituent of the liquid, which, though in solution, might be unable to pass through their pores, but simply by the subsidence of the corpuscles, which must have left all the materials of the liquor sanguinis behind them. Hence it is proved beyond question that if the liquor sanguinis could be separated completely from the blood-corpuscles it would resemble the fluid of hydrocele in being incapable of coagulation when shed into a cup.

Now this struck me as a very satisfactory and beautiful truth, inasmuch as it clears away all the old mystery of the distinction between inflammatory exudations and dropsical effusions. Dropsical effusions, exhibiting little disposition to coagulate, have been supposed to consist almost exclusively of serum, and the exudation of the entire liquor sanguinis has been regarded as the special characteristic of inflammation; and very unsatisfactory theories have been put forward by ingenious pathologists to account for this difference. But it now appears that a dropsical effusion, like that of hydrocele, is undistinguishable from pure liquor sanguinis.

Various dropsical effusions have been lately investigated with reference to their coagulability on the addition of blood-corpuscles by Dr. Schmidt of Dorpat, who finds that while they differ from one another in the amount of water they contain (just as is the case with serum filtered artificially through animal membranes under different degrees of pressure), yet they are all but universally coagulable. Schmidt has also carried the investigation further. He has found that by chemical means he can extract from the red corpuscles a soluble material which, when added to these exudations, leads to coagulation.

In other words, he shows that the corpuscles do not act as living cells, but by virtue of a chemical material which they contain, which can be used in the state of solution, free from any solid particles whatever. He found also that the aqueous humour made a dropsical effusion coagulate, and that the same effect was produced by a material extracted from the non-vascular part of the cornea. Hence he regards the blood-corpuscles as only resembling other forms of tissue in possessing this property. These observations are extremely interesting, if trustworthy; and that they are so I do not at all doubt, but having only read Schmidt's papers within the last day or two I have not yet had opportunity of verifying his statements.[1]

It remains to be ascertained what share the material derived from the corpuscles has in the composition of the fibrine. Schmidt inclines to the opinion that the fibrine is probably composed, in about equal proportions, of a substance furnished by them and one present in the liquor sanguinis. If this be true, the action of an ordinary solid in determining the union of the components of the fibrine may be compared to the operation of spongy platinum in promoting the combination of oxygen and hydrogen.

It may be asked, How comes it that when the blood of a horse is shed into a cup, the buffy layer coagulates as rapidly, or nearly so, as the lower parts rich in corpuscles?

This is indeed a question well worthy of careful study. We know that the liquor sanguinis left by the subsidence of the red corpuscles within a healthy vein is incapable of coagulating when shed, except in a slow manner, which is accounted for by the corpuscles that remain behind in it. Hence it appears that when the blood as a whole is shed into a glass, the agency of the ordinary solid leads the corpuscles to communicate to the liquor sanguinis, before they subside, a material or at least an influence which confers upon it a disposition to coagulate, though it still remains fluid for some time after they have left it. Just as we have seen that a very short time of action of the ordinary solid upon the blood as a whole is sufficient to give rise to coagulation, so we now see that, provided an ordinary solid be in operation, the presence of the corpuscles for but a little while is enough to make the liquor sanguinis spontaneously coagulable, though not immediately solidified. We shall see, before concluding, an illustration of the importance of this fact to pathology.

[1] Since this lecture was delivered I have verified an important observation made by Schmidt, viz. that a given amount of corpuscles causes complete coagulation of only a limited quantity of hydrocele-fluid. From this he draws the inference that the action of the corpuscles cannot be of the nature of fermentation—the coagulative efficacy of the corpuscles being not continued indefinitely, but becoming exhausted in the process of coagulation. For Schmidt's papers, see *Archiv für Anat. Phys.*, &c., 1861 and 1862.

It remains to be added that serous membranes resemble the lining membrane of the blood-vessels in their relations to the blood, as is implied by John Hunter's observation that blood which had lain for several days in a hydrocele coagulated when let out. The same thing is well illustrated in a frog prepared like this which I now exhibit. About four hours ago, a knife having been passed between the brain and cord to deprive the creature of voluntary motion in the limbs and trunk, the peritoneal cavity was laid open in the middle line, and its edges being kept raised and drawn aside by pins, I seized the apex of the ventricle of the heart with forceps and removed it with scissors. In a short time the whole of the animal's blood was in the peritoneum, and it may be seen that it is still fluid in spite of this long-continued exposure. When I first performed the experiment three years and a half ago, the weather being cool (about 45° Fahr.) and a piece of damp lint being kept suspended above the frog to prevent evaporation and access of dust, I found that the blood remained fluid in the peritoneal cavity for four days, except a thin film on the surface and a crust of clot on the wounded part of the heart ; but a piece of clean glass placed in the blood in the peritoneum became speedily coated with coagulum. Here, it will be observed, not merely the liquor sanguinis, but the corpuscles also were present in the serous cavity, yet no coagulation took place in contact with its walls.

I think it probable, though not yet proved, that all living tissues have these properties with reference to the blood. We know that the interstices of the cellular tissue contain coagulable fluid, and I have seen anasarcous liquid coagulate after emission, but this indeed may possibly have been merely liquor sanguinis coagulating in consequence of slight admixture of blood-corpuscles from the wounds made in obtaining it.

Looking now at the principal results which we have arrived at, it must, in the first place, be admitted that the ammonia theory is to be discarded as entirely fallacious. The fact that this theory is exceedingly plausible, and has been supported by many ingenious arguments and experiments, is of course no reason why we should retain it if unsound. On the contrary, the more specious it is the more necessary is it that it should be effectually cleared away, for it mystifies the subject of coagulation most seriously ; and I may say, for my own part, that it has cost me an amount of experimental labour of which the illustrations brought forward this evening convey but little idea. Still these have been, I trust, sufficient to show that the coagulation of the blood is in no degree connected with the evolution of ammonia, any more than with the influence of oxygen or of rest. The real cause of the coagulation of the blood, when shed from the body, is the influence exerted upon it by ordinary matter, the contact of which for a very brief period effects a change in the blood, inducing a mutual reaction between its solid and fluid constituents, in which the corpuscles impart to the liquor sanguinis a disposition to coagulate. This reaction is probably simply chemical in its nature, yet its product, the fibrine, when mixed with blood-corpuscles in the form of an undisturbed coagulum, resembles healthy living tissues in being incapable of that catalytic action upon the blood which is effected by all ordinary solids, and also by the tissues themselves when deprived of their vital properties.

These principles have, of course, very extensive applications to the study of disease, but I must content myself with alluding very briefly to inflammation, the most important of all pathological conditions.

If we inquire what is the great peculiarity of inflamed parts in relation to the blood as examined by the naked eye, we see that it consists in a tendency to induce coagulation in their vicinity—implying, according to the conclusions just stated, that the affected tissues have lost for the time being their vital properties, and comport themselves like ordinary solids. Thus, when an artery or vein is inflamed, coagulation occurs upon its interior, in spite of the current of blood, precisely as would take place if it had been artificially deprived of its vital properties. On one occasion I simulated the characteristic adherent clot of phlebitis by treating the jugular vein of a living sheep with caustic ammonia, and then allowing the circulation to go on through the vessel for a while, when, on slitting it up, I found its lining membrane studded with grains of pink fibrine which could be detached only by scraping firmly with the edge of a knife. Again, comparing an inflammatory exudation into the pericardium or into the interstices of the cellular tissue with dropsical effusions into the same situations, we are struck with the fact that, while the liquor sanguinis effused in dropsy remains fluid, the inflammatory product coagulates. Now we know that in intense inflammation the capillaries are choked more or less with accumulated blood-corpuscles, which must cause great increase in the pressure of the blood upon their walls; and from what we know of the effect of venous obstruction in causing dropsical effusion of liquor sanguinis through increased pressure, we are sure that we have in the inflammatory state the physical conditions for a similar transudation of fluid through the walls of the capillaries. And the natural interpretation of the difference in the two cases as regards coagulation seems to be, that whereas in dropsy the fluid is forced through the pores of healthy vessels, in inflammation the capillary parietes have lost their healthy condition, and act like ordinary matter; so that the liquor sanguinis, having been subjected, immediately before effusion, to the combined influence of the injured tissue and the blood-corpuscles, has acquired a disposition to coagulate, just like the buffy coat of horses' blood shed into a glass, or like the frog's liquor sanguinis filtered by Müller from its corpuscles, the injured vessels acting upon the blood like the filter.

This view of the condition of intensely inflamed parts is exactly that to which I was led some years ago by a microscopic investigation, the results of which were detailed in a paper that received the honour of a place in the *Philosophical Transactions*.[1] It was there shown, as I think I may venture to say, that the tissues generally are capable of being reduced under the action of irritants to a state quite distinct from death, but in which they are nevertheless temporarily deprived of all vital power, and that inflammatory congestion is due to the blood-corpuscles acquiring adhesiveness such as they have outside the body, in consequence of the irritated tissues acting towards them like ordinary solids.

I cannot avoid expressing my satisfaction that this inquiry into the coagulation of the blood has furnished independent confirmation of my previous conclusions regarding the nature of inflammation.

[1] 'On the Early Stages of Inflammation,' *Phil. Trans.*, 1858 (p. 209 of this volume).

ON ANAESTHETICS

[*Holmes's System of Surgery*, vol. iii, third edition. London, 1883.]

PART I. WRITTEN 1861

To prevent or diminish pain in surgical operations is an object so desirable, that many in various ages in the history of Medicine have sought to attain it, either by means of narcotic drugs designed to act on the body generally, or by compressing or otherwise locally affecting the nerves of the part concerned.[1]

The first really valuable suggestion, however, was made in the year 1800 by Sir Humphrey Davy, who, having himself experienced relief from pain when breathing nitrous oxide gas, threw out the hint that it might probably be employed with advantage to produce a similar effect in surgical practice.[2]

The same idea occurred, after the lapse of nearly half a century, to Dr. Horace Wells, a dentist in Hartford, Connecticut, who, in 1844, underwent the extraction of a tooth without pain after inhaling the gas, and gave it with satisfactory results to several of his patients ; but he soon after found the practice so uncertain that he abandoned it entirely.[3]

About the same period Dr. W. T. G. Morton, of Boston, in America, who had previously been a partner with Wells, but did not, as he informs us, receive any suggestion from him, became possessed with the desire of discovering an efficient anaesthetic, and commenced a series of experiments upon himself and the lower animals, which at last resulted in his extracting a tooth painlessly from a patient to whom he had administered the vapour of sulphuric ether by inhalation. This was on September 30, 1846.[4] Soon afterwards he publicly exhibited his method at the Massachusetts General Hospital ; and thenceforward anaesthesia in surgery was an established blessing to mankind.

Sulphuric ether is still extensively used as an anaesthetic in America, but in Europe chloroform is generally preferred to it. Disguised under the name 'chloric ether', in which it exists diluted with spirit of wine, this agent was the subject of Dr. Morton's first experiment upon himself ;[5] and it was

[1] For much curious information regarding the history of this subject the reader is referred to the work of the late Dr. Snow on *Anaesthetics*.

[2] *Chemical Researches*, p. 556.

[3] *Statements of William T. G. Morton, M.D., on his Claim to the Discovery of the Anaesthetic Properties of Ether*, &c. Washington, 1853, pp. 42 et seq.

[4] Dr. Morton's *Statements*, &c., pp. 45 et seq.

[5] Op. cit., pp. 45, 46.

used in the same form at St. Bartholomew's Hospital, in preference to sulphuric ether, by Mr. Lawrence in the summer of 1847.[1] In the autumn of that year Dr. (afterwards Sir James Y.) Simpson, who was engaged in a series of experiments with various narcotic vapours, employed for the first time the active principle of chloric ether, at the suggestion of Mr. Waldie, of the Apothecaries' Hall of Liverpool;[2] and finding that the pure chloroform was more potent than sulphuric ether, yet caused less bronchial irritation, while its odour was more agreeable, and its inferior volatility rendered its exhibition more easy,[3] he zealously recommended it to the profession, and it has since been generally employed throughout Europe.

The effects produced by chloroform are such as to fit it remarkably for the purposes of the surgeon. Like most narcotics, it tends to cause, after temporary excitement, suspension of the functions of the nervous centres, but affects them not simultaneously, but in a certain order; and the brain is the first to show loss of power in failure of sensation and voluntary motion. If this were all, anaesthesia would be a questionable boon, as the work of the surgeon would be interrupted and often marred by involuntary struggles on the part of the patient. But very soon the spinal cord also is subdued, and the reflex functions of the cerebro-spinal axis are abolished so far as concerns the voluntary muscles, which consequently lie perfectly relaxed and passive, better suited for operative purposes than the most resolute will could render them. To this, however, there is one remarkable exception, viz. that the parts concerned in the respiratory movements remain active; and the same is the case with the sympathetic ganglia of the heart. In other words, when the administration of chloroform is carried to a certain point, the nervous system is deprived of such powers as would cause pain to the patient or inconvenience to the surgeon, but retains intact the faculties essential to life.

There are, however, yet other advantages derived from the inactivity of the cerebro-spinal centre. It seems now clearly established that the cessation of the contractions of the heart in the shock of injury depends upon an action of the brain and cord upon the cardiac ganglia through the medium of the vagus and sympathetic nerves; and chloroform, rendering this action impossible, protects the heart from the indirect effect of external violence. In this way it has greatly diminished the risk of death upon the operating table, and also

[1] Snow on *Anaesthetics*, p. 20. That chloric ether was employed at St. Bartholomew's Hospital has been further confirmed by information kindly communicated to me by Mr. (now Sir James) Paget.

[2] Snow on *Anaesthetics*, pp. 21, 22; also Dr. Simpson's original pamphlet, *Account of a New Anaesthetic Agent*, &c., p. 6.

[3] For operations performed by artificial light, chloroform has another advantage over ether, in the fact that its vapour is not inflammable.

has overthrown the old rule of deferring amputation in cases of injury till the patient has recovered from the state of collapse, thus shortening the period of mischief to the system from the presence of the mangled limb, and in extreme cases sometimes saving life where it would be hopeless to wait for returning consciousness. Indeed, an amputation performed under chloroform has often the effect of improving instead of lowering the pulse.

The most striking instance of this that has fallen under my notice occurred in a labourer, whose right arm and thigh had been destroyed by a railway accident, just enough sound tissue being left to admit of amputation through the hip and shoulder joints, which was accordingly performed as a forlorn hope by the surgeon in charge of the case. The vital powers being in a state of extreme depression, it is probable that without chloroform this severe measure would have killed him outright, but by help of the anaesthetic it was followed by marked improvement of the pulse, which continued for some hours, so as to lead us to entertain hopes of his recovery.

Faintness during the operation, a species of shock, is also got rid of by chloroform ; and this, besides its obvious convenience, has the advantage of lessening the chance of secondary haemorrhage ; for the vessels which require ligature declare themselves as such by bleeding, instead of deceptively eluding observation in consequence of the feebleness of the heart and the general arterial contraction which coexist in the state of syncope.

The welfare of the patient is besides greatly promoted by the mental tranquillity arising from the prospect of immunity from suffering, which also induces persons to submit much more readily to the necessary operations, and often to undergo without hesitation treatment which was formerly impracticable because intolerable.

Such being the great benefits conferred by this agent, it is melancholy to reflect that in many parts of Europe, and even of the United Kingdom, it is either withheld altogether or given so scantily as to be nearly useless. This arises from fear, inspired by several fatal cases that have occurred. But when I state that Mr. Syme has given chloroform about five thousand times without ever meeting with a death, and that Sir J. Simpson's experience, also very extensive, has, so far as I am aware, been equally satisfactory, it is clear that it may be used so as to be practically free from any risk whatever.

How then are the fatal cases to be accounted for ? Heart disease has been supposed to be a common cause of them ; and it is a prevalent opinion that it is highly dangerous to administer chloroform to persons affected with cardiac disorder.

It happens that the only death I ever witnessed under chloroform occurred in a person whose heart proved, on examination, to be extensively affected with fatty degeneration, such as would be regarded as sufficient explanation of sudden death under any circumstances. The particulars of this case, however, presented peculiar features, which lead me to take a different view of the part played by the chloroform from what might at first be assumed. The patient was a man above the middle period of life, affected with cancer of the penis, for which amputation of the organ was to be performed. The gentleman in charge of the chloroform, considering the momentary nature of the operation, purposely abstained from giving it as fully as usual, and had removed the cloth containing it from the face before the operation was commenced. The surgeon now placed his finger on the patient's wrist, and having ascertained that the pulse was good, at once effected the amputation almost instantaneously. I observed that the passage of the knife through the member was accompanied by a start of the patient's body; the bandage used to control the bleeding was then removed, but no blood flowed from the arteries; he was found to have no pulse at the wrist; in short, he was dead. From these facts we can hardly doubt that death was a consequence of the shock of the operation acting on a diseased heart; and the only question is whether the circumstance that he had taken chloroform promoted that result. From the foregoing considerations such a thing seems altogether improbable, as we have seen that chloroform protects the heart from the effect of shock. The fact that the patient started proved that reflex action was not abolished in the voluntary muscles, and confirmed the statement of the administrator that the chloroform was imperfectly given. My own impression is, that if it had been pushed to the usual degree the fatal occurrence would have been averted.

I have given this case in detail because I believe it may be regarded as typical of a considerable class in which death has taken place suddenly at the commencement of an operation with imperfect administration of chloroform, which stands to the fatal event in the relation of an accidental concomitant, or rather a preventive insufficiently used[1].

A death essentially similar, though more obviously unconnected with chloroform, took place on the occasion when it was intended to have administered it for the first time in the Edinburgh Infirmary; but Dr. Simpson being prevented from attending, the operation was commenced without the anaesthetic, and the patient died suddenly immediately after the first incision. It has been often remarked that if the original intention had been carried out, chloroform would never have been heard of again in Edinburgh, but it is very likely that the man might then have lived to testify to its benefits.

There is another class of fatal cases in which the use of chloroform seems

[1] An observation made several years ago by Mr. Bickersteth, of Liverpool, has an interesting bearing upon this class of cases. He noticed on three occasions in amputation of the thigh that the pulse stopped suddenly at the moment the knife entered the limb, but recovered itself in a few seconds. The patients were under the influence of chloroform; but as Mr. Bickersteth never observed the same thing again, though he watched the pulse carefully at the same period in a great number of capital operations under chloroform, it seems probable that the anaesthetic was not administered to its full degree in those instances. (See *Monthly Journal of Medical Science*, September 1853.)

to have been simply a coincidence, the real cause of death being mental emotion, acting usually upon a disordered heart.

Dr. Snow mentions a distinct example of this, where a mere profession of administering chloroform was made, and the patient died of fright ;[1] and I am able to give, from Edinburgh experience, an instance in which chloroform was still more remotely concerned. The late Dr. Richard Mackenzie, being called to see a gentleman who had fractured his radius, had some thought of employing chloroform in examining the arm, but, changing his mind, made the necessary manipulations without it. He then proceeded to leave the house, but had not got down the steps leading from the door when he was called back with the announcement that his patient had suddenly expired.

Had chloroform been held near the face a few seconds before this occurrence, it would certainly have been blamed, though with manifest unfairness ; and a similar injustice seems to have been committed with regard to several cases in which fatal syncope has taken place early in the administration of the anaesthetic, when the brief period of inhalation concurred with the symptoms in showing that the patient was little, if at all, under its influence. A fear of the chloroform itself seems to have been the exciting cause in some of these cases ; and one reason why no such instance has occurred in the Edinburgh Infirmary is probably the unlimited confidence reposed in this agent by the inmates of that institution.

It might, perhaps, have been expected *a priori* that chloroform, in the early or exciting stage of its operation, would act upon a diseased heart like mental emotion, and cause irregularity or cessation of its contractions. This, however, does not seem to be the case ; and, judging from my own experience, I should say that it tends rather to remove intermission or irregularity of the pulse. On the whole I believe that chloroform, by preventing shock and mental effort during the operation as well as anxiety before it, is in reality a great source of safety in heart disease ; and that if a person with known cardiac affection decides to place himself in the hands of the surgeon, so far from being unsuited for the anaesthetic, he is before all others the man who stands most in need of its protecting influence.

Nevertheless, even when the heart is perfectly healthy, it is quite possible to administer chloroform so as to produce a directly sedative and deadly influence upon the cardiac ganglia. This truth was deeply impressed upon me eight years ago by the following occurrence.

An eminent London physician, desirous of making some experiments upon the heart, selected a young donkey for the purpose, and requested me to maintain artificial respiration, which was done by means of a large pair of bellows con-

[1] Snow on *Anaesthetics*, p. 201.

nected with a tube tied into the trachea, the animal having been previously put under the influence of chloroform. The chest having been opened, the investigation was continued for a while, when the creature began to exhibit signs of returning consciousness. To avert this I removed the bellows, and poured into them a considerable quantity of chloroform, and resumed the artificial respiration with energy for a short time, the natural respiratory movements meanwhile continuing ; when suddenly the heart, which lay exposed before us, ceased to beat, and refused to contract again even when its muscular substance was pinched, which showed that its nervous apparatus was paralysed.

This was no doubt caused by the air becoming highly charged with chloroform in passing over the extensive evaporating surface presented by the interior of the bellows. For it had been before shown by Dr. Snow, from experiments upon the lower animals, that an atmosphere containing more than a certain percentage of the narcotic vapour stops the heart before breathing ceases, whereas the reverse occurs when the chloroform is more diluted with air.[1] Hence, with the view of preventing fatal syncope, Dr. Snow contrived an inhaler for regulating the amount of chloroform vapour in the inspired air, and used it in upwards of four thousand cases, of which only one was fatal, and even that seemed to be so independently of the chloroform. Finding his ingenious efforts crowned with such success, and charitably supposing that all were as careful as himself, he concluded that fatal cases in the hands of others could result only from a faulty method of administration ; and assuming that when chloroform is given from a folded cloth it is apt to be in too concentrated a form, he attributed most of the deaths that have occurred to paralysis of the heart from this cause.

But the cloth being the means which has been used from the first in Edinburgh, with success even superior to Dr. Snow's, I have been long satisfied that his argument was fallacious ; yet as his special devotion to the subject, and the valuable facts which he has communicated regarding it, render his opinion influential, I have thought it worth while to subject a matter of such great practical importance to experimental inquiry ; and, about the usual quantity of the liquid being employed, I find that, so far from the amount of chloroform given off from the cloth being in dangerous proportion to the air inhaled, the whole quantity which evaporates from the under surface, even when the rate is most rapid, viz. just after the liquid has been poured upon it, is below Dr. Snow's limit of perfect security against primary failure of the heart.[2]

[1] I have noticed, however, that different animals differ in their susceptibility to chloroform. Thus frogs or mice may be kept for any length of time under its influence ; but bats are very apt to die when treated in exactly the same way.

[2] The experiments were performed in the following manner : A cloth, similar in all respects to what would be used in practice, was supported upon a light wire framework, and suspended at a little distance

But, considering the great diffusibility of the vapour, and the large amount blown away in expiration, it is evident that only a small proportion of that which comes from the lower surface of the cloth really enters the lungs. Were it otherwise, it would be extremely dangerous to give chloroform with the cloth to infants, for as they inhale but a small amount of air, they would then breathe the vapour in a very concentrated state; yet all are agreed that infants are peculiarly favourable subjects for chloroform. In truth, the quantity dissipated into the surrounding air when the cloth is used involves considerable wastefulness in this means of administration, which is its only disadvantage as compared with an inhaler, but this is abundantly compensated by its greater simplicity, and consequent greater safety. For any apparatus which has the effect of preventing the free access of the atmosphere must be liable to operate in the same deadly manner as the bellows in the case above related, and even when constructed upon the best principles, it will require most careful management, as is admitted by Dr. Snow with regard to his own inhaler.[1] On the other hand,

from the floor by a thread, connected with one end of the beam of a balance, projecting over the edge of the table on which it stood. The weight of the cloth having been ascertained, a weighed quantity of chloroform, corresponding to fl. ʒjss., which is about the amount commonly used, was poured upon the middle of the lower surface of the cloth, which was then allowed to hang close above my face, so that I might breathe fully upon it, while inspiration was performed through a long india-rubber tube to avoid inhaling the chloroform vapour. The amount lost by the cloth was indicated by the weights in the scale at the other end of the beam. At the commencement of an experiment the weight was made a few grains less than the sum of the weights of the cloth and chloroform together, and an assistant noted the second when the scale with the weights in it came to preponderate; then removed ten grains so as to allow the scale to rise, and again watched the time of its descent; and repeated this process several times, thus obtaining a very accurate record of the rate of alteration in the weight. The lower surface of the cloth, which was made slightly concave, was circumstanced just as in the early period of the administration of chloroform, except that the inspired air was drawn from a distance. Inspiration does not, however, materially affect the rate of evaporation, as was found by experimenting with a cloth arranged above the mouth of a tube into which air was drawn by an appropriate apparatus. Allowance being made for the slight gain in weight that the cloth would obtain from absorbing moisture from the breath, the amount of chloroform lost from both surfaces together was thus easily determined. In order to ascertain how much escaped from the upper surface, experiments were made with the same cloth, having first the upper and then the under side securely covered with oil-silk, the arrangements being as above described, except that my face was not below the cloth. The quantity given off from the upper surface in a normal atmosphere was thus determined; and this being subtracted from the whole loss from both surfaces under the circumstances of inhalation, gave the amount that evaporated from the lower surface only. At the temperature of 70° Fahr. this proved to be, from the average of several experiments, at about the rate of 24 grains per minute during the first half-minute; and allowing, with Dr. Snow, that 20 grains of chloroform correspond to 15·3 cubic inches of the vapour, and that 400 cubic inches of air are inhaled in a minute, we get 4·5 per cent. as the proportion of the chloroform to the inspired air, on the hypothesis that all that evaporates from the lower surface enters the lungs; 5 per cent. being what Dr. Snow was led by his experiments to regard as the proportion at which the respiration was quite sure to fail before the circulation, and that at which he aimed with his inhaler (op. cit., p. 34). On the other hand, Dr. Snow assumed that, when the cloth is used at a temperature of 70° Fahr., 9·5 per cent. of chloroform is really inhaled (op. cit., p. 34); whereas, in truth, of the 4·5 per cent. a large amount is dissipated into the surrounding air.

[1] Op. cit., pp. 181, 188.

there can be no mistake about the manner of using the cloth, which is also always at hand under all circumstances.

The theory of syncope from too great strength of the anaesthetic vapour when the cloth is employed being erroneous, the greater number of the deaths still remain unaccounted for ; and, if we except a very few instances for which we seem to have nothing to fall back upon but an idiosyncrasy so rare that it may practically be left out of consideration altogether, their explanation will, I believe, be found in an overdose of this potent narcotic from too long continued administration.

This is what might be expected from a general view of the statistics. Were we to ask ourselves in what sort of operations we should have anticipated most frequent deaths during the employment of chloroform, we should say in those which are likely to inspire great dread on account of their magnitude and severity, and to cause great shock and great haemorrhage. More especially should these preponderate among fatal cases in general hospitals, where serious operations constitute the majority of those performed. The reverse of this, however, is what we actually find. Of the whole number of cases recorded by Dr. Snow in 1858, as due to the use of chloroform throughout the world during ten years, nine only occurred in any considerable surgical procedure at a general hospital ; remarkably few, considering the enormous number of important operations that must have been performed during so long a period, and the variety in the qualifications of those who administered the chloroform. On the other hand, fourteen took place at similar institutions in connexion with the most trivial matters, such as the removal of a toe-nail, the amputation of a finger, the passing of a catheter, or the cauterizing of a wart. The only rational explanation of this seems to be, that when some great operation is to be performed, like the amputation of a thigh or the removal of a stone from the bladder, plenty of well-qualified assistants are present, and each of them, including the giver of the chloroform, is duly impressed with the importance of his office, and bestows the requisite pains upon it. But when some trifle is to be done, the whole affair is apt to be regarded too lightly, and the administration of the anaesthetic is perhaps confided to some unsuitable person, who also allows his attention to be distracted by other matters. This conclusion is entirely in accordance with my own experience, which, while it has convinced me more and more of the safety of chloroform if properly given, has impressed me deeply with the necessity for more vigilant care in its employment than is sometimes apt to be bestowed.

But an overdose of chloroform may be caused by attention misapplied, as well as by want of attention. The requisites for safety in using it will be best introduced by a short account of what ordinarily occurs in the mode of administration with which I am most familiar. A common towel being arranged so as to form a square cloth of six folds, enough chloroform is poured upon it to moisten a surface in the middle about as large as the palm of the hand, the precise quantity used being a matter of no consequence whatever. The patient having been directed to loosen any tight band round the neck, and to shut his eyes to protect them from the irritating vapour, the cloth is held as near the face as can be comfortably borne, more chloroform being added occasionally as may be necessary. After a time, varying considerably in different individuals, but generally longest in adults who have been accustomed to the free use of narcotics, and shortest in young children,[1] signs of excitement begin to manifest themselves in various ejaculations and muscular efforts, which soon give place to a state of complete repose. The struggles of the patient are sometimes so violent as to require considerable force to restrain them, and, for this reason, at least one efficient assistant should always be in attendance. On the other hand, I have seen chloroform induce nothing but a tranquil slumber ; and it is important to bear in mind that the stage of excitement cannot be reckoned on as invariably declaring itself at all.

The most convenient test of the patient being prepared for undergoing the operation is presented by the eye ; not in the size of the pupil, which is inconstant in its indications, but in what is commonly spoken of as insensibility of the conjunctiva, though in truth it has no relation to sensation, which is abolished considerably earlier ; but when unconscious winking no longer occurs on the eyeball being touched with the tip of the finger, we have a good criterion of the suspension of reflex action in the body generally. At this period the pulse is in about a normal condition, and the respiration is usually either natural or very slightly stertorous, though persons with a strong tendency to snore may do so almost from the commencement of inhalation. But if the administration of the chloroform be further persisted in, strongly stertorous breathing will soon be induced, and will become aggravated till it passes into complete obstruction to the entrance of air into the chest, though the respiratory movements of the thoracic walls still continue. Occasionally, however, the premonitory stertor is deficient, and the breathing becomes more or less suddenly obstructed. This is a point of great importance, for without close attention

[1] I once met with an instance in which chloroform seemed incapable of affecting a patient. It occurred in the private practice of Mr. Syme, who was about to perform an operation, for which we proceeded to administer the anaesthetic ; but after we had used the cloth till we were tired without any apparent effect, Mr. Syme went on with the operation while the patient was conscious. Such a case is, no doubt, excessively rare, but it is interesting as giving some colour to the hypothesis that idiosyncrasy in the opposite direction has existed in some very few fatal cases, which seem to admit of no other explanation, as alluded to in the text.

it may escape notice, when the patient will be placed in imminent peril. For though the respiration may be resumed spontaneously, this cannot be relied on, and it would seem that when chloroform is given in an overdose, the cardiac ganglia are apt to become enfeebled ; and on this account asphyxia produces more rapidly fatal effects under its influence than in ordinary circumstances. But if the obstructed state of the breathing is noticed as soon as it occurs, and the cloth is immediately removed from the face, and the tip of the tongue seized with a pair of artery forceps [1] and drawn firmly forwards, the respiration at once proceeds with perfect freedom, the incipient lividity of the face is dispelled, and all is well.

I am anxious to direct particular attention to the drawing out of the tongue, because I am satisfied that several lives have been sacrificed for want of it. In order that it may be effectual, firm traction is essential. I have, more than once, seen a person holding the end of the organ considerably beyond the lips without any good effect, and, placing my hand on his, have given an additional pull that has re-established the respiration.

A simple experiment, which any one may perform upon himself, is illustrative of this point. Stertorous breathing, such as occurs under chloroform, may be produced at will, and may be carried on even while the tongue is protruded to the extreme degree. But if the tongue is laid hold of with a handkerchief and pulled so as to cause decided uneasiness, stertorous breathing of any kind becomes impossible. That further traction, when extension already exists to the utmost, should produce such an effect is an apparent anomaly which it seemed important to explain. On investigating the subject, I noticed in the first place that stertorous breathing is of two essentially different kinds, of which one, that may be called *palatine*, consists in vibrations of the velum, and has either a buccal or nasal character, according as the air passes through the mouth or the nose ; while the other, which is the profound stertor essentially concerned with chloroform, depends on a cause seated further down the throat, and, for reasons to be given immediately, may be termed *laryngeal*. By digital examination of my own throat I found that the latter variety, and the complete obstruction into which it passes, could still be produced when the tongue was separated by a considerable interval from the back of the pharynx, while a free passage for the air existed onwards to the lips, which showed that the general belief, that the obstruction depends on a 'falling back of the tongue', is erroneous. Also the epiglottis, instead of being folded back during the

[1] The artery forceps are the most convenient means of drawing the tongue forwards. The puncture which they inflict is of no consequence ; the patient, if he notices it at all, supposes that he has bitten his tongue when under the chloroform.

obstruction, as some have supposed, had its anterior edge directed forwards; and though it was thrown into vibrations when the stertor was strongest, it was evident that the cause of the sound was more deeply placed. I also found that, although firm traction upon the tongue abolished the obstruction and the stertor, it did not appear to produce the slightest change in the position of the base of the tongue; nor did it move the os hyoides upon the thyroid cartilage, as examined from without. Hence I was led to conclude that the beneficial effect of this procedure could not be explained mechanically, but must be developed in a reflex manner through the medium of the nervous system. The fact that, when sensation is perfect, some degree of pain is caused in the process, implying an irritation of the nerves, was in favour of this view; while the general abolition of reflex action by chloroform did not seem strongly opposed to it, considering that the reflex respiratory movements, including those of the glottis, go on in a person under the influence of chloroform.

For further elucidation of the matter I had recourse to the laryngoscope; and, after a little patience, found no difficulty in inspecting my own vocal apparatus without employing any depressor of the tongue, using simply the small oblique long-handled speculum and a common mirror in bright sunlight. I then ascertained that the true laryngeal stertor results from the vibration of the portions of mucous membrane surmounting the apices of the arytaenoid cartilages, i.e. the posterior parts of the arytaeno-epiglottidean folds (thick and pulpy in the dead body, but much more so when their vessels are full of blood), which are carried forwards to touch the base of the epiglottis during the stertorous breathing, and are placed in still closer apposition with it when the obstruction becomes complete. Having one hand at liberty, I was able to observe the effect of drawing forward the tongue under these circumstances, and I saw that firm traction induced the obstructing portions of mucous membrane in contact with the epiglottis to retire from it for about an eighth of an inch, so as to allow free passage for the air, while the epiglottis itself was not moved forwards in the slightest degree.[1]

[1] While the true laryngeal stertor was thus produced and thus removed, a sort of spurious snoring might be made by approximation of the vocal cords; but this spurious stertor was, like the voice, quite unaffected by drawing out the tongue. These observations were made on September 21 of the present year (1861). I find that there are four ways in which the passage through the larynx may be closed. First, the folding back of the epiglottis over the opening into the pharynx, as is generally believed to take place in swallowing, and may be demonstrated by arresting an act of deglutition in its progress, and insinuating the finger between the tongue and the roof of the mouth to the epiglottis, which is then felt to be turned backwards, and to return to its usual position as the act of deglutition is finished. Secondly, an approximation of the *sides* of the superior orifice of the larynx, in which the epiglottis is directed forwards, but folded longitudinally, so that its edges are in contact with one another while the arytaeno-epiglottidean folds are also in lateral apposition. [Note written in April 1908: This fact was observed in the retching caused by the application of a solution of nitrate of silver

Whether pulling the tongue operates by inducing or relaxing muscular contraction in the larynx may be matter for discussion, but the main conclusion, that it does not act merely mechanically, but through the nervous system, appears satisfactorily established. I have not hesitated to give the evidence on which it rests in full, as it appears to me to be of the highest practical moment. For it shows at once how grievous a mistake is committed by those who content themselves with gently drawing the apex of the tongue a little beyond the teeth, or pushing forward its base with the finger, or perhaps ascertaining that the epiglottis is not folded back. Such proceedings are instances of attention misapplied, and waste the golden opportunity for rescuing the patient from death. The proper treatment, like many other good things in medical practice, owes its origin to a false theory, but though the erroneous notion of obstruction by the tongue did good service in the first instance by suggesting the original method, it now tends to encourage supposed improvements upon it, which rob it entirely of its efficacy.

If the above description is correct, if it is true that when the administration of chloroform with the cloth is carried too far, the first serious symptom is an obstructed state of the respiration, which without watchful care may occur unnoticed, and, if allowed to continue, will endanger the life of the patient, but, if promptly treated, will harmlessly disappear—it follows that the attention of the administrator ought to be concentrated on the breathing, instead of being, as it too often is, diverted by the pulse, the pupil, or other matters still less relevant.

As an example of the risk that is run by want of close attention to the respiration I may mention the following case. A surgeon of considerable experience was giving chloroform to a patient on whom an operation was being performed, of which I was a mere spectator, but I noticed that stertorous breathing came on, and gradually passed into complete obstruction, at a time when the administrator was gazing with interest upon the proceedings of the operator. Seeing that the patient was in danger, I suggested to the giver of the chloroform the propriety of pulling forward the tongue. He replied that this was uncalled for, and pointed to the heavings of the chest as evidence that

to the larynx of a patient. I find that it is not universally recognized.] This occurs in retching, and doubtless also in vomiting, when a folding back of the epiglottis, instead of protecting the larynx, would tend to direct into it the material passing from below upwards. Thirdly, an *antero-posterior* coaptation of the structures of the laryngeal aperture at a somewhat deeper level, without any change in the position or form of the epiglottis, towards which the folds of mucous membrane above the apices of the arytaenoid cartilages are carried forwards, till they are in contact with its base. This is seen in coughing, and also in laryngeal stertor; and it is probable that during sleep, when the respiration is so apt to become stertorous, there is but a very narrow chink between the epiglottis and these folds of mucous membrane, which would thus serve to protect the deeper parts of the air-passages from the introduction of foreign matters in the state of unconsciousness. Fourthly, the closure of the *rima glottidis* in the production of voice. The white *chordae vocales* form a beautiful contrast with the highly vascular structures in their vicinity.

breathing was proceeding freely. Knowing from what had gone before that those efforts were doing nothing for the respiratory function, and feeling that there was no time for discussion, I stepped out of my province so far as to seize the tongue myself and draw it forward, when a long and loudly stertorous inspiration demonstrated the necessity for the interference. Had the delusive movements of the chest been trusted, it is probable that they might have continued till the heart had become so enfeebled by the asphyxial state as to cause no perceptible pulse at the wrist ; and had death occurred under these circumstances, the case would have been set down as one in which the circulation failed before the respiration. The administrator would thus have been absolved from all blame, and the fatal event would have been attributed to idiosyncrasy, or to any heart disease which might have been discovered on post mortem inspection.

The very prevalent opinion that the pulse is the most important symptom in the administration of chloroform is certainly a most serious mistake. As a general rule, the safety of the patient will be most promoted by disregarding it altogether, so that the attention may be devoted exclusively to the breathing. The chance of the existence of heart disease may seem to make this practice dangerous, but having followed it myself with increasing confidence for the last eight years, and knowing that it has been pursued all along by Mr. Syme, who has also acted on the maxim that every case for operation is a case for chloroform, and must, therefore, have given it to very many patients in whom cardiac disorder existed unknown to him, besides some in whom its presence had been ascertained, I feel no hesitation in recommending it. Even when serious disease of the heart is known to exist, it must be remembered that there is much less risk of syncope than of obstruction to the respiration ; and while the latter will demand and repay immediate attention, the former, should it by any chance occur, being in all probability independent of any excess of chloroform, would not imperatively demand its discontinuance ; nor would it be much influenced by treatment, supposing the patient to be already in the horizontal posture, which is generally considered safest in all cases when chloroform is given.[1]

From these considerations it appears that preliminary examination of the chest, often considered indispensable, is quite unnecessary, and more likely to induce the dreaded syncope, by alarming the patient, than to avert it.

[1] From the views expressed in the text regarding the relation of syncope to the administration of chloroform, it might be inferred that no great danger would be incurred by giving it in the sitting posture when circumstances particularly require it ; and accordingly Dr. Snow informs us that he has done this on several occasions without any bad result. But considering the possibility of an overdose, and the feebleness of the heart which that seems to entail, it is no doubt wisest, as a general rule, to have the patient reclining. Dentists, it is true, give chloroform in the sitting posture ; but, so far as I have seen, they do not carry the administration beyond a slight degree, sufficient to deaden sensation without affecting reflex action, dexterously managing to open the mouth and operate upon it while the muscles of the jaws are rigid.

The obstructed state of the breathing, if allowed to continue long, would lead to a far more serious affection—paralysis of the nervous centre concerned in the respiratory movements. Pulling out the tongue would then of course have no good effect of itself, but it should be done to clear the way for artificial respiration, which is the means to be essentially trusted to under such circumstances; and if the air still fail to enter freely into the chest, an opening ought to be made without delay through the crico-thyroid membrane. Cold water should also be occasionally dashed upon the face and chest; and if a galvanic battery happen to be in readiness, one of its poles may be applied over the spinous processes of the upper cervical vertebrae, and the other to the praecordial region, with the object of rousing the respiratory and cardiac ganglia. This, however, is a means not very likely to prove beneficial, and if used in too intense a form it may do harm instead of good.

Preparatory to taking chloroform the patient should be directed to omit the last meal which would naturally precede it, as any food in the stomach is almost sure to give rise to troublesome vomiting during the inhalation. The only after-treatment necessary is to allow the effects of the chloroform to pass off in a quiet sleep; and the only bad consequence likely to arise is a tendency to sickness, which sometimes causes annoyance during the first twenty-four hours or so.[1]

Chloroform is universally applicable in the various departments of surgery, except in some few cases in which the assistance of the patient is required, and in operations involving copious haemorrhage into the mouth. Blood may trickle in small amount into the pharynx without risk of choking, deglutition being carried on unconsciously during anaesthesia; and even in some instances when the bleeding is more serious, as in removing portions of the jaws, pain may be avoided to a great extent by giving the chloroform during the more superficial parts of the operation, and allowing the patient to recover partially before undertaking its deeper stages.

The main conclusions arrived at in this article may be expressed in a few words. It appears that chloroform, though resembling many other valuable means of treatment in being deadly when mismanaged, is free from danger

[1] It has been supposed by some that the use of chloroform increases the risk of pyaemia after capital operations; but experience has now abundantly proved the groundlessness of this apprehension. To take a single instance, the veins of the pelvic viscera being perhaps, next to those of the bones, more liable than any others to originate phlebitis after surgical interference, lithotomy would be much more fatal now than formerly were there any foundation in fact for the notion. The reverse, however, appears to be really the case. Thus, Mr. Cadge, one of the surgeons of the Norfolk and Norwich Hospital, an institution long celebrated for the successful treatment of stone, in a district abounding in calculous disease, informs me that the mortality after lithotomy has been still further reduced there since the introduction of chloroform.

if properly used, the following being the rules for its safe administration. A drachm or two of the liquid having been sprinkled upon the middle of a folded towel, hold it near the face, taking care that free space is afforded for the access of air beneath its edges, till the eyelids cease to move when the conjunctiva is touched with the finger. Meanwhile watch the breathing carefully; and if at any time it should become obstructed or strongly stertorous, suspend the administration and draw the tip of the tongue firmly forwards till the tendency to obstruction has disappeared.

These simple instructions may be acted on without difficulty by any intelligent medical man. The notion that extensive experience is required for the administration of chloroform is quite erroneous, and does great harm by weakening the confidence of the profession in this valuable agent, and limiting the diffusion of its benefits.

Part II. Written 1870

The nine years which have passed since the above article was written have tended to confirm its main doctrines.

The safety of chloroform when administered according to the rules laid down in the preceding pages has hitherto been verified without exception in my own personal experience; and I may add that Mr. Syme, though he continued to within the last two years in the full activity of his career as an operator, never lost a patient through its use, either in public or private practice. Further, I believe I am correct in stating that no case of death from chloroform has occurred during these nine years in the operating theatre of either the Edinburgh or the Glasgow Infirmary, two of the largest surgical hospitals in Great Britain. Yet in both these institutions a folded towel on which the anaesthetic liquid is poured, unmeasured and unstinted, is still the only apparatus employed in the administration; preliminary examination of the heart is never thought of, and during the inhalation the pulse is entirely disregarded; but vigilant attention is kept upon the respiration, and, in case of its obstruction, firm traction upon the tongue is promptly resorted to. And it is worthy of special notice, as showing that success is due to soundness of the principles acted on, rather than any particular skill, that the giving of the chloroform, instead of being restricted to a medical man appointed for the function, as is elsewhere often thought essential, is entrusted to the junior officers of the hospital. In Edinburgh each of the five surgeons has two 'clerks', intermediate in position between the house surgeon and the dressers. They, besides other duties, take it in turn to administer the anaesthetic; and if I had to be placed under its influence I would rather trust myself to one of these young gentlemen than to the great majority of ' qualified practitioners '.

The appointment of a special chloroform-giver to a hospital is not only entirely unnecessary, but has the great disadvantage of investing the administration of chloroform with an air of needless mystery, and withholding from the students the opportunity of being trained in an important duty, which any one of them may be at once called upon to discharge on commencing practice, and which, though certainly simple, is better performed after some practical initiation. I well remember the anxiety I felt on entering upon office as Mr. Syme's house surgeon, though I had before held a similar position in London, lest his first fatal case should occur in my hands ; but this feeling soon gave place to perfect confidence, more especially after I had seen symptoms, which would before have alarmed me, dispelled at once by traction on the tongue, which was then a novelty to me, and which is, I fear, even yet not duly appreciated by the profession generally.

An incident which occurred during my Glasgow incumbency illustrates so strikingly both the value of drawing forward the tongue, and the relations of the circulation and the respiration to chloroform, that it seems right to place it on record. One of my colleagues in the Infirmary had been making an attempt to reduce a dislocation by means of the pulleys, chloroform having been given very fully by the house surgeon, who, at the close of the performance, removed the cloth from the patient's face, and proceeded to attend to other matters. Happening to be present, and observing that the respiration was deeply stertorous, I watched it carefully, and noticed that it passed almost immediately into the state of complete obstruction, though still accompanied by the movements of the thorax, the face meanwhile becoming markedly livid. Unwilling to interfere, and seeing the carotid pulsation conspicuous in the neck, I waited awhile, hoping that the obstacle to the breathing would disappear spontaneously. But instead of this I soon saw to my horror the lividity give place to what I knew was physiologically identical with post mortem pallor. I now rushed forward and drew the tongue out firmly with the artery forceps ; air at once passed into the chest, and the man was rescued.

This case seems to me fraught with the deepest instruction.

There can be no doubt that the patient was on the very verge of death ; that if the laryngeal obstruction had lasted a very short time longer, the respiratory and cardiac ganglia would have failed in their functions. Supposing the administrator to have continued the chloroform with his attention devoted to the circulation, the first thing that would have alarmed him would have been the failure of the pulse at the wrist. On removing the cloth from the face, he would have seen the deadly pallor, and, ignorant of the asphyxial lividity which had preceded, he would have taken it as positive evidence of primary failure of the heart, a verdict in which the whole profession would probably have supported him, whether valvular disease or fatty fibres could or could not be discovered on post mortem inspection. The case, then, reads us another striking lesson on the paramount importance of taking the respiration as our guide, and shows how readily, if this be not done, a death due to the grossest mismanagement may be regarded as the inevitable result of constitutional peculiarity.

The case also shows the necessity of keeping watch for a while after the administration has been discontinued. The last portions of the vapour inhaled seem to take some seconds at least before they produce their full effects on the nervous centres ; and the patient should not be left till he has been seen to breathe calmly and freely for some minutes after the cloth has been removed.

On one occasion only, so far as I remember, have I seen firm traction on the tongue fail to remove laryngeal obstruction. In that instance the chest continued to heave, but no air entered or escaped, although the tongue was well drawn out. Happily, however, the desired effect was instantly produced by slapping the face with a towel dipped in cold water, while the traction on the tongue was maintained. This fact is interesting, not only as a striking illustration of the value of the sudden application of cold under such circumstances, but also because it confirms the explanation before given of the *modus operandi* of traction on the tongue, viz. that it operates not mechanically, but through the nervous system. For here the barrier to the entrance of air into the chest remained in spite of the clearing away of any obstacle which the tongue might be supposed to present, but that barrier was at once removed by a means which could not act in any other way than through the nerves.

It is nevertheless true that the tongue does frequently fall back under chloroform, and so occasion a mechanical impediment to respiration. It recedes, no doubt, in consequence of relaxation of the lingual muscles ; and accordingly thick or obstructed breathing depending on this cause may be very simply cleared by pulling the beard or forcibly pushing up the chin, so as to draw forward the tongue through the medium of the muscular fibres which pass back to it from the maxilla. Turning the patient's face well round to one side, so as to cause the weight of the relaxed organ to tell laterally rather than backwards, is another way in which a needless puncture of the tongue may often be avoided. But it must always be borne in mind that neither of these means can be expected to succeed if the obstruction exists in the larynx, and if they do not answer their purpose, not a moment should be lost in applying the artery forceps.

Whenever it is necessary to draw the tongue forward, it is of course equally needful to suspend the administration, by taking the cloth entirely away from the neighbourhood of the face. To act otherwise would be to pour in a fatal dose after artificially removing the natural safeguard against its entrance. To give a caution against so obvious a breach of physiological principle may seem superfluous, but I know by experience that it is not uncalled for.

I have admitted in the foregoing article that idiosyncrasy may have been the cause of death in some anomalous cases which have been put on record. We certainly see strange varieties in the effects produced by chloroform both on the cerebral and the spinal centres. Some persons when inhaling it lie from first to last as in a tranquil slumber ; some, before they succumb to its narcotic influence, struggle with great violence, without uttering a sound ; others bawl lustily, while some sing sweetly, and others again are disposed to converse quietly though incoherently with those around them. There are also remarkable differences in the relation of sensation to consciousness under chloroform. As a general rule they are affected simultaneously, but we now and then see patients insensible to the pain of an operation, though perfectly conscious of all that is passing. Equally various are the effects upon the spinal functions. The absence of winking when the eyeball is touched with the finger, though a very good general guide to the abolition of reflex action in the body generally, is by no means an unvarying indication. In some persons that particular function is abolished earlier or later than usual. Relaxation of the sphincters of the bowel and bladder is a result of chloroform happily only occasionally met with, and various other instances of exceptional phenomena might be mentioned. Another example of peculiarity, more closely bearing upon the question of death from chloroform, has come under my observation in two instances during the last nine years, viz. cessation of the movements of the thorax, or in other words suspension of the function of the respiratory ganglia, without any preliminary laryngeal obstruction, although there was not, so far as I could judge, anything unusual in the mode of administration. In both cases natural breathing soon returned under artificial respiration maintained by intermitted pressure on the false ribs, while the tongue was drawn forward, accompanied by occasional slapping of the face and chest with a cold wet towel. But the condition was sufficiently alarming while it lasted. The patients were both elderly, feeble subjects, and I may remark that if I ever give chloroform with any degree of apprehension, it is to the aged and infirm.

Another closely allied instance of idiosyncrasy once presented itself in my practice. I had removed under chloroform a small epithelial cancer from the eyebrow of a feeble old woman, nothing unusual having occurred, when I noticed that the breathing assumed a peculiar sighing character, and the intervals between the sighs became greater and greater, till I began to fear their entire cessation. However, normal respiration returned, and in the course of a few minutes she got up and sat in a chair beside the fire. But she had not been there long before the same strange slow breathing came on again, as if she would sigh her life away, and I believe that if I had not had her put back promptly to bed she would actually have died. Here a feeble frame was further weakened by the potent narcotic, and it happened that the effect told especially upon the respiratory function, with the peculiarity that it was manifested not during the administration of the chloroform, but subsequently.

With these examples before us of deviations from the usual order in which the various functions of the nervous system are affected by chloroform, no one can say it is impossible that here and there an individual may be found so constituted that, without any undue proportion of the narcotic vapour to the air inhaled, the cardiac ganglia may fail before the respiration is interfered with. But while freely admitting that such a thing is possible, I must repeat my firm conviction that this kind of idiosyncrasy is certainly 'so rare that it may practically be left out of consideration altogether'.

The danger of chloroform may be compared, not inaptly, to that of railway travelling. In both cases the risk incurred by any individual is so small that it does not enter seriously into our calculations. And just as railway accidents are generally occasioned by culpable mismanagement, so death from chloroform is *almost invariably* due to faulty administration.

Various attempts have been made during the last nine years to improve our anaesthetic methods. Among these must be mentioned the reassertion of the claims of sulphuric ether by the late Dr. Mason Warren, of Boston, in America. Our transatlantic brethren naturally feel indignant that their grand discovery of anaesthesia in surgery should be confounded with the very secondary matter of finding out that a different agent from that which they employed will produce similar effects in a more efficient manner. For the introduction of chloroform, when the whole subject was a novelty, led to a confusion in the public mind in this country, where 'the discovery of chloroform' is often regarded as identical with the discovery of anaesthesia. And there can be no doubt that if sulphuric ether were still in use in Britain as it is in Boston, and if chloroform were now brought forward for the first time as a substitute for it, comparatively little would be thought of the innovation. More convenient chloroform undoubtedly is, on account of its smaller bulk, and the greater facility of its administration, but Dr. Warren contended that these advantages were more than counterbalanced by the greater safety of ether, which he declared had never up to the time of his writing produced a single death.[1] Admitting

[1] See *Surgical Observations, with Cases and Operations*, by J. Mason Warren, M.D., &c.

the facts to be in the main as Dr. Warren has given them, the case may probably be fairly stated by saying that ether, being less potent, is less liable to cause death from mismanagement. But the rules for the satisfactory use of chloroform are so simple that mismanagement is really inexcusable ; and if we had nothing else to consider than the question of safety, chloroform would probably in all cases maintain its superiority over ether. There is, however, another point in which a great advantage has been lately claimed for the original anaesthetic. The vomiting which is so frequent after chloroform is generally only a matter of more or less inconvenience. But in the special case of ovariotomy the disturbance of the abdomen thus occasioned is thought to have sometimes been the cause of death. Dr. Thomas Keith, whose remarkable success in that operation is well known, was led to try sulphuric ether, in the hope that it might prove less objectionable in this respect, and the result has been in the highest degree satisfactory, so that whereas with chloroform vomiting was the general rule, it now seldom occurs in his practice.[1] Dr. Keith has also ascertained that if truly anhydrous ether be employed, it can be given so as to produce its effect almost as rapidly as chloroform, and without waste of the material, by simply pouring a little of the liquid occasionally upon a piece of flannel contained in a cup-shaped vessel adapted to the mouth and nose, with a small aperture for the entrance and exit of air. Hence, as there are various other operations in which the avoidance of vomiting is a matter of great moment, sulphuric ether seems likely to reassume an important place as an anaesthetic.

Nitrous oxide, which we had looked upon as of mere historical interest, as a kind of pioneer in anaesthesia, has also been revived of late years and turned to practical account, chiefly through the exertions of Dr. Evans, an American dentist residing in Paris. It is a remarkable fact, that when inhaled unmixed with atmospheric air, it fails to produce the excitement to which it owes the name of 'laughing gas', but merely throws the patient very rapidly into a condition of complete coma, attended with great lividity of the face, and staring dilatation of the pupils, presenting a very alarming appearance when seen for the first time, but, as experience shows, free from danger, subsiding as rapidly as it supervened, and leaving in the great majority of cases no trace of sickness or other unpleasant effects. The agent has recently been rendered much more portable by keeping it stored in the liquid form in a strong cast-iron bottle, from which, by turning a stopcock, the gas is supplied to an india-rubber bag, large enough to contain about an average dose for producing insensibility. When this is exhausted, the balloon can be refilled in the same way as often as may be desired, and thus it is possible by a series of intermitted administrations

[1] See *Lancet*, August 20, 1870.

to keep a patient under the influence of the gas for a protracted period. It is questionable, however, whether nitrous oxide, if employed for producing long-continued insensibility, would prove as safe as chloroform, and it is pretty generally admitted that its legitimate place is for operations of very short duration. But for avoiding the brief but acute agony of tooth-extraction it appears to be an unquestionable boon to humanity.

The benumbing influence of cold was brought into requisition several years ago by Dr. James Arnott for producing local anaesthesia, by means of a freezing mixture of pounded ice and common salt.[1] The same object has since been more efficiently attained by Dr. B. W. Richardson, by ingeniously availing himself of the reduction of temperature occasioned by evaporation. Anhydrous sulphuric ether intimately mingled with air in the form of spray is projected upon the part by means of a suitable apparatus easily worked by the hand. In a few seconds the skin upon which the spray plays suddenly assumes a snow-white colour, implying that its surface is completely frozen. It is well to continue the application for a little while after this change has occurred, in order to ensure the penetration of the effect to a sufficient depth. The frozen parts may then be incised or operated on in any way that may be desirable, without the slightest pain to the patient, and the tissues when thawed are generally as well disposed for healing as usual.

This method is necessarily of limited application. It is only adapted for superficial operations, and even for many of these the rigidity of the tissues occasioned by congelation is inconsistent with efficiency of performance, as in removing epithelial cancers, where the sense of touch is the principal guide for the surgeon ; or, again, in taking away thin-walled atheromatous cysts, where looseness of the surrounding cellular tissue is essential to satisfactory dissection. Nevertheless there are many cases, such as the incising of a boil or the removal of the nail of the great toe, in which this means of producing local anaesthesia proves perfectly satisfactory. In operating on the extremities I have found great advantage from restraining the circulation with a tourniquet, so as to prevent the oozing of hot blood, which would otherwise interfere with maintaining the frozen condition or extending it to deeper parts.

Part III. Written 1882

Since Part II of this article was written, twelve years ago, ether, on account of its supposed greater safety, has to a large extent superseded chloroform in the practice of many British surgeons. At the same time the manner of

[1] See *Lancet*, October 30, 1858.

administering it has undergone a remarkable change. Instead of a free admixture of atmospheric air, such as is essential to safety in giving chloroform, partial asphyxia is systematically combined with the toxic influence of the anaesthetic, by making the patient breathe over and over again the same air contained in a balloon of caoutchouc, a reservoir of ether being interposed between the balloon and a closely fitting mask over the mouth and nares. This may for convenience be termed the *close* method of administering ether, as distinguished from all varieties of what we may call the *open* method, in which fresh air is admitted with each inspiration. It was introduced by Dr. Ormsby of Dublin, and was brought to great perfection by the late Mr. Clover. Various advantages are claimed for it. It certainly greatly economizes the ether, and brings the patient very rapidly under its influence. It is also said that by utilizing the warmth of the expired air, and thus diminishing the great coldness of the inspired air occasioned in the open method by the rapid evaporation of the ether, it prevents a chilling of the lungs which sometimes led to serious and even fatal after-effects in the form of acute bronchitis or pulmonary oedema or congestion.[1] There can be no doubt that this constituted a real danger of the open method. A striking example of death taking place unusually rapidly from this cause is given in the *Lancet* of April 1 of the present year (1882) from a report furnished by Dr. Parsons, of New York, in whose practice the case occurred. A healthy woman, fifty-four years old, had ether given for the reduction of a dislocation of the shoulder of five weeks' standing, the operation lasting twenty-five minutes.[1] She took the ether well, about 6 fl. ounces being administered. Five minutes after reduction was effected she took some water, and about an hour and a half later Dr. Parsons left her apparently well. After the lapse of another half-hour, however, the house surgeon found her cyanosed ; and in spite of active stimulating treatment she died in the course of another hour. On post mortem examination the organs generally were found healthy, but the lungs were deeply congested. No mention is made of the mode of administration, but from the quantity of ether used we may infer that it was some form of the open method. Such occurrences are not generally published, but they would appear to be by no means very uncommon. A case of death from acute bronchitis after an operation on the eye for which ether was given by the open method was mentioned to me lately by a surgeon in whose practice it occurred, and who had no hesitation in attributing the fatal result to the ether. Mr. Hodges, of Leicester, writing in the *Lancet* of July 15, 1882, says : 'As regards deaths from ether, I make no doubt many occur which are never reported, for the simple reason that the death, instead of being instantaneous (as in the case of

[1] See Teale, *British Medical Journal*, March 11, 1882.

chloroform), occurs some hours later from bronchitis. At any rate, there have been two such deaths from ether at the Leicester Infirmary during the last nine years, against two from chloroform in the same period. It is scarcely necessary to remark that a fatal event brought about in this manner, though less appalling, is as much a death from ether as if it occurred on the operating table.

It would not be right, however, to look upon the close method as simply the open method deprived more or less of the risks attendant on chilling of the lungs. The close method is, as before remarked, a combination of partial asphyxia with etherization, and constitutes a new departure in anaesthesia which must be judged of independently.

From experiments which have been performed upon some of the lower animals it has been inferred that there is an essential difference between ether and chloroform as regards their action upon the heart: that whereas chloroform, after a brief period of stimulation, depresses it, ether for a long time fails to produce any lowering influence, or even acts as a persistent cardiac stimulant,[1] and this has been held to afford clear proof of the greater safety of ether.

There can, however, be no doubt that any agent capable of producing anaesthesia must, if continued in operation for a considerable time, exercise a lowering effect upon the whole vital powers. Ether, moreover, has its own special risks. Its vapour has an irritating effect upon the air-passages, such as is not caused by chloroform. Hence it increases the bronchial secretion, and tends to produce asphyxial complications, so that even its warmest advocates do not advise its employment when the respiration is seriously embarrassed, as in chronic bronchitis or emphysema. But asphyxia, even when carried to a minor degree, has a depressing effect upon the circulation; and accordingly on reading reports of death from ether, we often find it stated that the pulse and breathing ceased simultaneously.

In the close method of administration, anaesthesia being only partly brought about by the ether, asphyxial complications due to the action of the ether *per se* are necessarily less than in the open method. But, on the other hand, the partial asphyxia by which the action of the ether is supplemented in the former method, has a lowering effect upon the circulation. Hence a stimulating action of the ether upon the heart can by no means be reckoned on when this method is employed. On the contrary, the pulse may become, within a very short time, greatly reduced in force. This is illustrated by the instructions which accompany Mr. Clover's smaller inhaler as supplied by Messrs. Krohne and

[1] See Report of a Committee of the Medico-Chirurgical Society, *Med.-Chir. Trans.*, vol. xlvii, 1864, p. 335.

Sesemann, in which the following sentences will be found : ' If any interruption in the breathing occur, or *if the pulse should be indistinct* ' (the italics are mine), ' the face-piece need only be removed for one inspiration. The dark colour of the blood is a less reliable test of the need of air than the symptoms mentioned.' We cannot, therefore, be surprised to find that occasionally death takes place under this method of administration by primary failure of the heart.

In the *British Medical Journal* for July 15 of the present year Mr. Lawson Tait has put upon record what seems a perfectly clear example of such an occurrence. The patient, aged forty-five, was sent to Mr. Tait to be operated on for a large abdominal tumour. She was at first very anaemic and feeble, but improved in the hospital, so that it was decided to proceed to operation. She was placed under ether by means of Ormsby's inhaler, but before complete anaesthesia had been produced, Mr. Tait, who was observing the pulse, noticed that it had disappeared. Meanwhile ' the breathing was perfectly regular and deep '. The inhaler was at once removed, but in spite of artificial respiration, with lowering of the head, the breathing rapidly failed. ' Death took place at the heart at least one minute before the respiration was interfered with.' On post mortem examination the right side of the heart was found filled with clot, and the left side empty. The muscular substance was not distinctly diseased, but the organ was unusually small.

As a matter of physiological theory, supposing the heart to be diseased, and therefore liable to have its rhythmical action suspended by comparatively trivial disturbing causes, we could well understand that the unusual labour thrown upon the right side of the organ by asphyxial impediment to the pulmonary circulation might prove extremely serious, even in spite of a stimulating action of the ether upon it.

With regard to chloroform I fear some of the more recent experiments upon the lower animals have had an injurious practical tendency. Since the time of Dr. Snow we have understood that there is a most important difference in the effects of chloroform according to the proportions in which the vapour is mixed with the air inhaled : that when it is present in a concentrated form, it acts as a deadly sedative upon the heart, but that when largely diluted with the atmosphere, this effect is no longer observed, but if the agent is pushed far enough to cause death, the respiration probably fails before the circulation.

Yet in the experiments conducted by the Committee of the British Medical Association appointed to inquire into this subject, the question of the proportion of the anaesthetic to the air seems to have been entirely neglected. Starting with the assumption that chloroform, from its depressing influence upon the heart, is more dangerous than ether, while ether is much less convenient for administration, the attention of the Committee was chiefly directed to an endeavour to discover some agent intermediate between them in these respects ;

and such they found, as they believed, in ethidene dichloride, which they accordingly recommended as preferable to either of the others. But in order to ascertain the relative effects of the different substances upon the heart they used them all in a very concentrated form, the air being in many of the experiments made to bubble through the liquid contained in a Wolfe's bottle on its way to a tube tied into the trachea ; so that, to quote the words of the Committee, 'the air passed into the animal's lungs was saturated with the vapour of the substance used.' [1] Hence these experiments, though very interesting from the new facts which they elicited regarding 'ethidene', and valuable as respects ether, by showing that it may be safely given, so far as the heart is concerned, in a very concentrated form, have really little bearing upon the use of chloroform in the human subject, where it is well understood that the agent must be given largely diluted with air.

But these researches, by placing before the profession in an exaggerated form the effects of chloroform as a cardiac sedative, have tended to foster the idea that if chloroform kills, it always does so from the heart, and that the pulse is the main thing to be attended to in its administration.

Against this pernicious error I have endeavoured in the earlier parts of this article to raise an emphatic protest. I have pointed out how liable the breathing is to become obstructed under chloroform, whether by the falling back of a relaxed tongue or by closure of the valve of mucous membrane which guards the orifice of the larynx ; and, further, how obstruction from either of these causes may occur without premonitory stertor, in an insidious manner requiring the utmost vigilance for its detection ; so that, unless the attention is fixed upon the respiration, mere heaving of the chest and abdomen (which will continue long after air has ceased to enter the lungs), though doing nothing for the respiratory function, may be mistaken for effective breathing, the patient meanwhile being exposed to the serious dangers which attend a combination of asphyxia with the effects of chloroform. On the other hand, I have contended that if the breathing is carefully observed, and the obstructions referred to are removed as soon as they occur, due care being taken to avoid pushing the agent beyond what is needful to produce its anaesthetic and relaxing effects, the chloroform being given well mixed with the air by means of a folded towel held loosely over the face, all fear of primary failure of the heart may be dismissed from the mind.

The experience of the last twelve years has confirmed me in the soundness of this doctrine ; and I venture to think it not undeserving of careful consideration that in my hospital cases I have still entrusted the administration of the

[1] See 'Report on the Action of Anaesthetics,' &c., *Brit. Med. Journ.*, December 18, 1880, p. 957.

chloroform, not to a specialist or to a person of very large experience, but to a succession of senior students, changing from month to month, whose only qualification for the duty is that they must previously have served the office of dresser, and that they strictly carry out certain simple instructions, among which is that of never touching the pulse, in order that their attention may not be distracted from the respiration. I have also systematically abstained from making any preliminary examination of the heart, thus avoiding needless alarm, which we know to have been the cause of some fatal events both with chloroform and with ether.[1] Such has been my practice since I first obtained the office of full surgeon to a large hospital twenty-one years ago, and I have never had reason to regret it.

During this long period I have often operated upon patients known to be affected with disease of the heart, and among the rest there must necessarily have been included many affected with fatty degeneration of its muscular fibres, which is regarded as the most formidable condition with reference to chloroform.

It happened not long ago that an elderly lady, whose mamma I removed for scirrhus, died a few days after the operation from the singular complication of perforation of the duodenum by an ulcer caused apparently by the irritation of gall-stones. She had taken the chloroform quite well, but I found on post mortem examination that the heart was affected with as extreme a degree of fatty degeneration and at the same time thinning of the ventricular walls as I could well imagine to be consistent with the maintenance of the circulation.

Such being my own experience, and well knowing how apt the administrator is to fail to notice the insidious obstruction of the respiratory passages, I cannot help believing that in many of the cases reported in the journals where primary failure of the heart is stated to have occurred, mere respiratory movement without respiratory function has been mistaken for true breathing continuing after cessation of the pulse.

It is, alas ! true that I can no longer speak of never having had in my own experience a death occasioned by chloroform. One unmistakable instance of this fearful calamity occurred lately in my private practice. But the circumstances were such as seem to me to preclude the idea of syncope. They were as follows :—

A strong, healthy man, twenty-seven years of age, came under my care with a lumbar abscess unconnected with the vertebrae. I proposed to open it under chloroform, which was administered from a folded towel. The patient struggled rather more than usual during the administration, which had not been carried to

[1] For an instance of death from fright at the commencement of the inhalation of ether, see *Brit. Med. Journ.*, November 17, 1877 ; case reported by Dr. Lowe, of Lincoln.

the degree of producing muscular relaxation when he began to make a spurious snoring or snorting noise, which is generally a sure indication that the patient requires more chloroform. Mr. Watson Cheyne, who was giving the chloroform for me, had, however, removed the cloth from the face, and I was about to remark that this was an unnecessary precaution, when the patient fell into a sort of epileptiform condition, attended with a state of spasm of the respiratory muscles and wide dilatation of the pupils, while the face was deeply livid. As no respiratory movements were going on, I had him drawn up on the table so as to make the head dependent, and commenced artificial respiration, while the tongue was drawn forward with artery forceps. The chest, however, seemed fixed in the state of expiration, so that compression of the thorax caused no escape of air, while the drawing up of the arms equally failed to cause the entrance of any. I have frequently performed artificial respiration, but never before met with such a state of things. Cold water was dashed upon the chest and abdomen, and, whether as a consequence of this or not, two spasmodic acts of inspiration took place, separated by a considerable interval. I opened the trachea, but in the condition of the thoracic walls which I have described, this procedure was in itself completely futile. Some little time having been lost in vain attempts at artificial respiration, I passed down the trachea from the wound a piece of wide india-rubber tubing several inches long, and by blowing into this succeeded in inflating the lungs, as was indicated by rising of the abdomen and very slight elevation of the ribs, and I continued artificial respiration in this way for about half an hour in vain. The pulse had been observed to be good just before the occurrence of the alarming symptoms. What its condition was during their presence we were too much occupied to ascertain ; but the great lividity of the face, and indeed of the whole body, clearly indicated that the heart continued to drive imperfectly oxygenated blood through the vessels long after the respiration had been arrested by muscular spasm. We obtained permission to examine the heart twenty-four hours after death, and found its muscular substance abundant and healthy, and its valves all competent. With the exception of some spots of slight opacity on the mitral valve, it was a thoroughly healthy heart. Its cavities contained fluid blood ; and this escaping on the removal of the organ from the body, the relative amount in the cavities of the two sides was not ascertained. I afterwards learned that the patient had been in a state of extreme terror at the prospect of taking chloroform ; and I suspect that this may have been the cause that determined the occurrence of the strange state of nervous excitement which proved fatal to him. By a curious coincidence it happened that the medical man who recommended this patient to my care, on learning of our disaster, wrote to me stating that a short time previously he had met with a very similar state of epileptiform spasm of the respiratory muscles in a man in whom he was examining a simple fracture without chloroform. It lasted so long that my friend considered that it was on the verge of proving fatal. Of course in my case the chloroform was the cause of the fatal event, but my impression is that it would have been as likely to happen under any other anaesthetic.

Quite recently the subject of the different effects produced by an anaesthetic, according to the proportion which it bears to the air in which it is diffused, has been brought forward in an exceedingly striking manner by Monsieur Paul Bert. Experimenting in a manner essentially similar to that adopted by Dr. Snow, diffusing various quantities of the anaesthetic in air contained in a vessel of known capacity, so large as to avoid all chance of asphyxial complications, he has arrived at remarkable conclusions. So far as I can gather from the very brief account which he has published (*Comptes Rendus*, Nov. 14, 1881), he concludes that there is a certain percentage below which chloroform fails to produce any anaesthetic effect, however long it continues in operation; that there is another percentage, at or above which it proves mortal ('l'animal finit par mourir'); and that between these two definite proportions there is a 'workable zone' ('zone maniable') which produces anaesthesia, but does not kill; and when the quantity of chloroform is such as to be about the middle of this *zone maniable*, the animal is rapidly anaesthetized ('il est très rapidement anesthésié'), and yet may be safely left for an indefinite time in the same atmosphere (the experiment was sometimes continued as long as two hours), 'sans qu'on ait à s'occuper ni à s'inquiéter de lui.' Curiously enough, the smallest mortal proportion was just double the smallest anaesthetic quantity; and this held for all kinds of animals, although the absolute amount differed for different species. And the same law obtained with ether, bichloride of methylene, and other anaesthetics which were made the subjects of experiment.

These views are so startling that, if it were not for M. Paul Bert's high scientific reputation, we should be disposed to disregard them altogether. There can, however, be no doubt of their great importance if correct, and I have endeavoured to test their accuracy by some experiments similar to his with one of the species which he employed, viz. the mouse, and though my experience is very limited, being confined to results obtained from a single family of white mice, yet it seems deserving of mention.

There were four young ones just ready to leave their dam, and I found, as Dr. Snow had done, that the young animals of this species were more tolerant of chloroform than the adult. The creature was in every case introduced into a large glass jar of known capacity, containing air through which a certain percentage by weight of chloroform had been thoroughly diffused, assuming one hundred cubic inches of air to weigh thirty-one grains, which for practical purposes was sufficiently accurate.

Seven per cent.,[1] which is the middle of Paul Bert's *zone maniable* for the mouse, proved much too strong for my animals, causing complete arrest of the breathing in one of the young ones in a quarter of an hour, though it recovered on being at once withdrawn from the chamber. An adult, the father of the

[1] It is to be borne in mind that the percentage by weight is a totally different figure from the percentage by volume used by Dr. Snow and adopted in Part I of this article, the vapour of chloroform being 4·2 times heavier than air.

family, was killed by the same percentage in four minutes, and, the chest being at once opened, the heart was found to have entirely lost its irritability, failing to contract when pricked with a needle. This percentage, then was clearly within Paul Bert's mortal zone for these white mice. Four per cent. (4.9 being the extreme lower limit of Paul Bert's *zone maniable* for the mouse) caused complete anaesthesia in three minutes and a half in another of the young animals ; and this atmosphere being continued in operation produced a progressively lowering effect upon the breathing, which was reduced in the course of one hour and twenty minutes from two hundred per minute to twenty-eight shallow and irregular respirations, after which the animal died. The heart was, however, found beating when the chest was opened twenty minutes later, and the exposed organ continued to pulsate even for another hour, showing how little its power had been affected by the chloroform in the more diluted state.

The experiments being continued on the following day, three per cent. of chloroform rendered one of the young animals completely passive in two minutes and a half ; and within four minutes it had brought the respirations down to seventy-eight, and in the course of one hour and three-quarters reduced them to about twenty feeble and irregular movements, after which they ceased entirely, and did not recur, although the animal was withdrawn from the chamber within two minutes and a half of their cessation. The more rapid anaesthesia and greater depression of the respiration occasioned by this smaller percentage of chloroform are, I believe, to be explained by a feeble state of the animal, caused by its having been the subject of the first experiment on the previous day. The fact illustrates the different susceptibilities to chloroform that may be presented by the same individual under different circumstances.

Two per cent., tried with another of the young mice, made the animal stagger in about two minutes, but failed to produce complete anaesthesia in an hour ; and at that time the respirations continued as high as one hundred and sixty per minute. But after the lapse of another hour anaesthesia was found to be complete, and the respirations reduced to eighty-six. In the course of two hours more the breathing was further lowered to fifty-six, and it was evident that death would occur in no long time if the animal were kept in the same atmosphere. It was removed, and recovery took place, but only very slowly, no movement of the limbs showing itself for nearly an hour.

Lastly, a percentage intermediate between those of the last two experiments was tried, viz. two and a half. It produced anaesthesia somewhat slowly in the young animal subjected to it, requiring a quarter of an hour for complete relaxation. The respirations meanwhile had come down from about two hundred to one hundred and sixty-eight, and, after the lapse of twenty-two minutes more, had fallen to one hundred and four. The animal was now left unobserved in the chamber for another hour, and at the end of that time it was found dead. It will be observed that two and a half per cent., though it anaesthetized more slowly, yet killed sooner than four per cent. had done on the previous day. The subject of the experiment had, I fear, been weakened by being kept in less favourable hygienic conditions since it was got from the dealer the day before.

The facts elicited by these experiments, though not numerous, seem to me instructive. In the first place, they afford an illustration of Dr. Snow's important principle, that there are two essentially different ways in which chloroform may kill, viz. by a directly sedative action on the heart when the chloroform is in large proportion to the air, and by a suspension of the respiratory function, while the heart is still acting, when the chloroform is largely diluted. They also show how different individuals of the same species, and even the same individual at different times, may differ in susceptibility to chloroform. And in the third place they indicate, I fear, but too plainly, that we cannot by any means trust implicitly to the existence of Paul Bert's three distinct zones. For we have seen that a proportion of chloroform which produced anaesthesia so extremely slowly that, if it was within the anaesthesic zone at all, it must have been at its very lowest limit, nevertheless exerted a gradually increasing deleterious influence, tending at last to a fatal result. And when the proportion was increased so as to make any approach to the 'very rapid' anaesthetizing effect which, as M. Bert tells us, characterizes the middle of the *zone maniable*, a similar but more rapid deleterious action was observed, causing death considerably within the two hours referred to by M. Bert. We see, therefore, that, for those animals at least, there existed no efficiently anaesthetic mixture of chloroform and air, which could safely be left in continuous action for such a length of time as is not unfrequently occupied by a surgical operation.

Hence, whether we regard the various degrees of susceptibility to chloroform shown by different individuals, or the sure though gradual lethal effects of even the smallest proportion which suffices to be anaesthetic, I fear the proposal which I understand M. Bert to make, that the *zone maniable* having been ascertained for man, a corresponding atmosphere should be provided in a large reservoir, from which the patient should be allowed to inspire continuously throughout the duration of an operation, must be rejected as highly dangerous.

But, although I have thus failed to verify M. Paul Bert's precise conclusions, yet I believe we owe him a deep debt of gratitude for his researches. The experiments which I have conducted on the lines which he has laid down have made manifest an important truth entirely new to me. I had always supposed that a chloroform atmosphere sufficiently strong to produce anaesthesia would, if continued, soon lead to a fatal result. Such certainly is apt to be the case with chloroform administered by means of a folded towel. It once fell to my lot to see a patient who had been left for only a few minutes with the cloth lying over the face after full anaesthesia had been produced, in consequence of the attention of the administrator having been distracted by other matters, and I shall never forget the result. Respiratory movements had entirely ceased, and the face had a deadly pallor, and for a while it appeared as if the patient was dead, though happily revival took place after protracted artificial respiration.

And I have seen other patients thrown into a condition of distinct peril from the same cause carried to a minor degree. Yet we have seen in the experiments above recorded that, even in animals which seem to have been peculiarly sensitive to the action of chloroform, atmospheres which produced anaesthesia in a very few minutes did not cause death till they had continued in action considerably more than an hour. Those atmospheres had the peculiarity of being on the one hand, extremely mild, and, on the other hand, constant in quality ; and, assuming that effects more or less closely analogous would follow in the human subject, it is clear that we ought to make a systematic attempt to attain them. If for the fitful mode of administration by the folded towel, with atmospheres perpetually oscillating between the needlessly strong and the uselessly weak, we can substitute a method which shall give a uniform and at the same time a mild anaesthetic air, we may anticipate very beneficial results. The avoidance of the needlessly strong atmospheres can hardly fail to diminish the chances of mishap from inadvertence, and this in two ways : first, by making respiratory embarrassments less likely to occur ; and, secondly, by rendering it far less dangerous to continue the administration of the anaesthetic when the patient is fully under its influence. An equable exhibition of the drug will also save time, and thus not only promote the convenience of the surgeon, but also the comfort of the patient, since the after-effects of the narcotic are more or less proportioned to the length of the period during which it has continued in operation.

Moreover, the facts which M. Paul Bert has elicited may well embolden us to continue a steady administration of the chloroform after the patient has been brought fully under its influence. For we know that, when complete anaesthesia has been brought about, a very much smaller proportion of the chloroform is needed for the maintenance of that state than was required for its production : all that is necessary being to supply enough to compensate for the elimination of the drug by the lungs and other emunctory organs. Hence, if an atmosphere of the mild but constant character referred to, while effective for the rapid production of anaesthesia, may in the lower animals be continued for an hour or more of full strength without causing death, it seems only reasonable to anticipate that, if the greatly reduced proportion that suffices for maintaining anaesthesia were substituted when the patient had been fully subdued, it might be steadily continued without danger for any length of time that might be desirable. And I need hardly remark on the convenience that would result from such an arrangement, as compared with the liability to partial recovery with its attendant struggling in the middle of an operation, when chloroform is given from the folded towel by any but very experienced administrators.

But there is reason to believe that other important advantages will be gained by more uniform administration. It would appear that there are serious objections to allowing the patient to recover from time to time from the effects of the chloroform. Dr. Kirk of Glasgow made, several years ago, some interesting observations bearing on this subject, which have not yet been published, but which he kindly allows me to refer to. He found that if a cat was placed in a jar containing an anaesthetic mixture of chloroform with air, and removed when it was only partially anaesthetized, and at once examined with the stethoscope, the pulse always made a sudden and considerable rise from the depression which the chloroform occasioned, and not unfrequently this rise was followed by a complete suspension of audible cardiac pulsations, lasting it might be for an entire minute. If, however, the animal was retained in the jar till complete anaesthesia was effected, such suspension of pulsation was never observed. I am not aware that anything exactly corresponding has been observed in the human subject. But I have often seen great pallor precede vomiting under chloroform, and it seems probable that this vomiting, and the depression which accompanies it, have been due to the fitful way in which we have been in the habit of giving chloroform with the folded towel. For Dr. Kirk, who has paid great attention to this subject, informs me that he has never seen vomiting occur under chloroform except during recovery from the anaesthesia. And this experience is strikingly confirmed by Mr. Meredith, of the Samaritan Hospital, who tells me that he avoids vomiting during ovariotomy by giving chloroform with Junker's inhaler, in which air is driven by Richardson's hand-bellows through a bottle of the liquid, and thence into a vulcanite mask over the mouth and nose, where it mixes freely with pure atmospheric air inhaled through a valve in the mask. In this way the chloroform is given in a mild and very uniform manner till the patient is fully anaesthetized, and afterwards any approach to recovery is anticipated by the occasional use of the bellows. And not only is vomiting prevented during the operation, but the further highly satisfactory result is obtained that the patient is not affected to any material extent with the after-sickness which formerly proved so serious in ovariotomy, and induced Dr. Keith to abandon chloroform in favour of ether.

Vomiting under anaesthesia is a serious matter, requiring prompt attention in the way of turning the head well to one side, in order to avoid the risk of vomited matter passing into the larynx. Ether seems more liable to cause vomiting during actual anaesthesia than chloroform, and several of the deaths under ether which have been published have been from this cause. But after-sickness appears to be much more frequent and more distressing with chloroform administered by means of a folded towel than with ether; and it will be a great point gained if this serious drawback, together with the depression that attends it, can be got rid of.

Junker's inhaler acts admirably in experienced hands, but the working of the bellows is a somewhat irksome business ; and there is, besides, the great disadvantage of a special apparatus which may not be always at hand, and which, if not in frequent use, is liable to get out of order. And I cannot but think that, if the valve of the mask is not properly managed, there will be danger of the chloroform being given in too concentrated a form.

A much more simple way of giving chloroform in a continuous and equable manner is that of dropping it frequently, by means of a drop-bottle, upon a flannel bag stretched over a wire frame, as was, I believe, first suggested by the late Dr. Skinner, of Liverpool. The drop-bottle may be very simply made by providing an ordinary bottle with a second cork traversed by a piece of glass tube sufficiently small in calibre to allow only one or two minims to escape at once when the bottle is momentarily inverted. Special drop-bottles of more durable and convenient construction may be got from the instrument-makers ; but for an emergency a cork, with a small notch cut out of one side, introduced into a common bottle, will answer the purpose sufficiently well. By these means chloroform may be given in a very steady, continuous manner ; and some who are accustomed to this method speak very highly in its favour. But Dr. Skinner's bag is needlessly large ; and from this circumstance, and also from the very accurate manner in which it applies itself to the face by means of an elastic band at its orifice, it must be apt, unless cautiously used, to accumulate too large a quantity of chloroform ; and I know that deaths have occurred under its use.

A much smaller frame is also sold by the instrument-makers, with a correspondingly smaller flannel bag, fitting, like Skinner's, accurately to the face. This apparatus proved on trial amply adequate, anaesthesia being very rapidly induced, with extremely little consumption of chloroform. But, even though so much smaller, the closely fitting bag seemed to me liable to the danger of giving the chloroform too strong, especially when the breathing is shallow. I therefore made trials with a piece of flannel stretched over the small frame, but having an interval of about half an inch between its border and the skin of the face ; and I found that a piece with an area of nine square inches arranged in this way, and kept constantly moist with chloroform, failed to induce anaesthesia within a reasonable time in an adult male, but answered the purpose well if a piece of rag was thrown lightly round the interval between the flannel and the skin, so as to check, but not altogether prevent, the flowing away of the heavy vapour of the chloroform. Thus I seemed to have arrived at an arrangement as near the lower limit of efficiency as was possible. And as there is no special virtue in flannel, as compared with a single layer of linen of coarse texture, I substituted for the frame and flannel the corner of a towel, pursed up systematically into a concave mask to cover the mouth and nose by pinching it together at such a distance from the corner that, when the pinched-up part is held over the root of the nose, the corner extends freely to the point of the chin.

The cap formed in this manner being so arranged upon the face, chloroform is gradually dropped upon it till the greater part of it is soaked, the edges being left dry to avoid irritation of the skin by the liquid ; and the moist condition is maintained by frequent dropping until the requisite physiological effects are produced ; the respiration being at the same time carefully watched with a view to the instant adoption of the measures described at p. 144 in case of any obstruction to the free entrance of air. When full anaesthesia has been produced, it is steadily maintained by dropping with about half the frequency : for I find that half the quantity of chloroform per minute that is used for producing anaesthesia is not far from the amount required for maintaining it. Any one accustomed to giving chloroform with the folded towel or compress has to learn to avoid the two extremes of applying the drop-bottle too seldom, and putting on too much chloroform at a time.

In giving chloroform in this manner, it is of great importance to bear in mind that the amount inhaled is proportioned to the surface which is moistened, so that it would not be right to use an indefinitely large piece of towel for the purpose. When the cap is made as above directed, large enough to extend freely from the root of the nose to the point of the chin, the part which is moistened during the production of anaesthesia has an area of about nine square inches (that of a circle three and a half inches in diameter) in the case of the adult male. But the apparatus is self-adjusting in so far that the cap varies in dimensions with the face, which, again, is more or less proportioned to the size of the body ; and thus, for example, a very much smaller evaporating surface is provided for a young child than for an adult. It is further self-regulating in this respect, that when the breathing is shallow, and the quantity of air to be mixed with the chloroform consequently diminished, the percentage of the chloroform is not correspondingly increased, because a much smaller amount evaporates under those circumstances than when the air is moved freely over the cloth in deep inspiration ; and further, when the vapour is not drawn into the chest, its density causes it to flow away under the loose margins of the cap, instead of accumulating as it would do under a closely fitting bag.

When the surface of the towel is restricted as above recommended, the proportion of chloroform to the air inhaled is extremely small. In order to estimate this proportion, it is necessary to ascertain, on the one hand, how much chloroform enters the lungs per minute, and, on the other hand, how much air is inhaled during the same period. The former element is obtained as follows :—The drop-bottle being graduated, the quantity of chloroform employed for the production of full anaesthesia is determined by inspection, and the number of minutes which have elapsed during the process is also noted. The amount of chloroform which is known to be necessary to moisten the cap being subtracted from the whole employed gives the quantity which has evaporated from both surfaces during the time of administration ; and this divided by the number of minutes gives the total evaporation per minute. Then, allowing with Michael Foster that inspiration occupies about four-elevenths of the whole respiratory period, this fraction of the total evaporation per minute is that which was given off from both sides of the cap per minute during inspiration. But this does not all really enter the lungs : a certain quantity of the heavy vapour, particularly of that which comes from the upper surface, falls away unconsumed, and this loss cannot be considered less on the average than a third of the quantity given off from both surfaces during inspiration, so that two-thirds of that amount is approximately the quantity of chloroform inhaled per minute. In order to form an estimate of the quantity of air with which this chloroform is mixed, I have carefully ascertained, by simple means which I need not here describe, the number of cubic inches expired per minute by myself and also by a healthy woman of about the average stature, both during tranquil breathing in the recumbent posture and during the shallowest respiration which it was possible to maintain for a minute together, so shallow, indeed, as to produce serious discomfort from the *besoin de respirer*. I also tried in my own case the product of full breathing. The results were as follows :—

For myself.

Deep respiration gave	1350 cubic inches per minute.
Tranquil respiration gave . . .	540 ,, ,,
Shallowest possible respiration gave .	200 ,, ,,

For woman of about average stature.

Tranquil respiration gave	360 cubic inches per minute.
Shallowest respiration gave . . .	235 ,, ,,

From these figures we can form a fair estimate of the amount of air taken into the lungs per minute in any given case of administration ; and allowing 31 grs. for every 100 cubic inches, we calculate the percentage by weight of the chloroform to the inspired air, bearing in mind, of course, the relation of the specific gravity of chloroform to the fluid measure employed. To take two illustrations from actual practice :—A tall, middle-aged man of pretty stout build was brought into a state of full anaesthesia in 4 minutes by means of 1⅔ fl. drachms of chloroform, or 138 grs. ; 25 grs. would be about the quantity of chloroform remaining on a cap of the size used in his case, and if we allow 450 cubic inches as the amount of air breathed per minute—and this is a moderate estimate—a calculation made as above indicated gives 4·9 as the percentage of chloroform by weight in the inspired air, or 1·17 by volume. Again, a woman, below the average stature and slightly built, was completely anaesthetized in 4½ minutes by means of 1¼ fl. drachms of chloroform, or 104 grs. : and supposing that 15 grs. remained on the considerably smaller cap used in her case, and that she breathed 300 cubic inches per minute, we obtain 5·2 as the percentage of the chloroform by weight, or 1·2 by volume. The mildness of these atmospheres will be apparent when I state that M. Paul Bert's *zone maniable* was, for the dog, from 7·3 to 15·3 per cent. by weight, or 1·7 to 3·5 by volume, and for the mouse, from 4·9 to 9·8 by weight, or 1·2 to 2·33 by volume, so that the atmospheres used in the two cases referred to were considerably below the *zone maniable* for the dog and only just at the lower limit of that for the mouse. Or the point will perhaps appear still more strikingly when it is borne in mind that 5 per cent. by volume was that which Dr. Snow employed with his inhaler, and 3½ per cent. by volume that which was recommended as the average atmosphere by the chloroform committee of the Medico-Chirurgical Society.[1] Even in the case of extremely shallow breathing, an atmosphere as strong as that recommended by the committee would probably never be reached by this method. Persons less amenable to chloroform than the average yield to these mild atmospheres if they are longer continued. Thus a lady who had often taken chloroform from the folded towel or compress, and had been with some difficulty brought under its influence, was subdued in the course of 7 minutes by means of 2½ fl. drachms, or 207·5 grs., of chloroform. She was rather a large woman, and allowing that 20 grs. were required for moistening the towel, and that she breathed 400 cubic inches of air per minute, we find by calculation that the percentage of chloroform which she inhaled was 5·3 by weight, or 1·26 by volume. On another occasion, a somewhat larger cap being employed, she was anaesthetized in 4 minutes with 2 fl. drachms, or 166 grs., of chloroform, giving a percentage of 6·4 by weight, or 1·5 by volume. These are samples of several administrations in her case, and I observed that when the milder atmospheres were used she was free from the short fit of laboured and spasmodic breathing which invariably occurred when the larger cap with its stronger atmosphere

[1] Vide *Med.-Chir. Trans.*, vol. xlvii, p. 353.

was employed. This may have been a mere coincidence, but it seemed to indicate that the milder atmosphere, though more tedious in operation, was the safer. But in cases which must be expected from time to time to arise, in which the system is unusually tolerant of chloroform, when several minutes have passed without any apparent effect being produced, there can be no objection to making the cap somewhat larger, provided the administrator bears distinctly in mind that he increases the strength of the chloroform atmosphere in proportion as he enlarges the cap.

To return for a moment to the last case mentioned, I have to add that, although she required more chloroform than the average of patients for the production of anaesthesia, yet when this had been effected, it was maintained by the steady use of a comparatively small amount. Thus on one occasion she was kept perfectly tranquil for 12 minutes during what would have been very painful procedures by the use of $2\frac{3}{4}$ fl. drachms of chloroform, giving a percentage of 3·75 by weight or ·89 by volume, which is certainly an exceedingly mild atmosphere.

This method is a little more troublesome than our old plan of holding a folded towel over the face, and replenishing it with chloroform at considerable intervals ; but the constant attention which it necessitates is an additional element of safety. During the last five months I have proceeded on these principles, and I have been much pleased with the results. The gradual manner in which the chloroform is applied in the first instance makes the administration extremely comfortable to the patient ; respiratory obstruction has been markedly less frequent than formerly, even the falling back of a relaxed tongue being of rare occurrence ; there has been, as a rule, remarkable immunity from vomiting or after-sickness, and, except in one instance, no serious depression.

This exceptional instance deserves detailed mention on account of the illustration which it affords of an important point in the preliminary management of the patient. I operated on a delicate boy, twelve years of age, on account of the dislocation of the upper end of the radius forwards of many years' standing, removing the head of the bone and returning what remained to its natural position, an operation of short duration, and attended with scarcely any haemorrhage. Splints having been applied to keep the bone in position, the chloroform was discontinued, when some tendency to vomiting showed itself. While in this condition he was lifted into bed, and immediately on this being done he fell into a state of collapse, which was for a short time sufficiently alarming. The explanation of this most unusual occurrence appeared to be afforded by the neglect of my orders that he should sleep the previous night at the house where the operation was to be performed at nine a.m., and have a cup of tea, without bread, at seven o'clock to stay the stomach ; a practice which I have for many years adopted. It was only after the operation that I was informed that he had taken nothing whatever since five o'clock the previous afternoon, and that he had only been brought that morning to the house after a pretty long journey through London. This exertion, with prolonged fasting, combined with his weakly condition, sufficiently accounted for the symptoms of depression. While it is desirable that there should be no solid matter in the stomach when chloroform is administered, it will be found very salutary to give a cup of tea or beef-tea about two hours previously.

If chloroform carefully given in the simple manner above recommended is really as safe a means of producing prolonged anaesthesia as we possess, a conviction that such is the case will be a great relief to the majority of our practitioners throughout the country ; all special apparatus being avoided, and selection of cases needless. For chloroform, if we are once satisfied of its safety, has the grand advantage that it may be used alike for the infant and the aged, and for those affected with pulmonary, cardiac, or renal disease. Wherever an anaesthetic is demanded, chloroform is applicable.

For the treatment of alarming symptoms of collapse, whether due to idiosyncrasy in the patient or to want of due watchfulness in the administrator, the practice suggested by Nélaton has proved of the greatest value. It is sometimes spoken of as ' inversion ' ; but all that is essential is to place the head at a considerably lower level than the body generally. Of the practical efficacy of this treatment no doubt will be entertained if we bear in mind the relief afforded in faintness by placing the patient in a horizontal position, or, if he be sitting, by depressing the head to the level of the knees ; or, again, the converse fact of the occurrence of syncope on a patient sitting up for the first time after a long and weakening illness. On mere hydraulic principles, indeed, the beneficial effect of inversion would be inexplicable ; seeing that gravity, being equally balanced in the arteries and veins, cannot of itself promote the flow through the blood-vessels, except in so far as the increased pressure due to that cause might lead to their distension and so to diminution of friction ; while in the special case of the brain the enlargement of the vessels as a whole would be effectually prevented by the circumstance of the organ being enclosed in an unyielding box. But we know, from observations which I have published elsewhere,[1] that when any part of the body is raised, its arteries, large and small, are thrown into a state of contraction through the vaso-motor nervous system ; and conversely, when a part is placed low, its arteries become freely relaxed

[1] See an address on the Influence of Position on the Local Circulation, *Brit. Med. Journ.*, June 21, 1879, reprinted at p. 176 of this volume.

through the intervention of the same nervous agency, out of all proportion to any effect which the increased pressure of the blood upon their walls through gravity could occasion. We therefore understand how 'anaemia of the brain', or languid flow through constricted arteries, may be caused by unwonted elevation of the head, and how relaxation of the cerebral arteries, and correspondingly free flow of blood through them, may be induced by placing the head unusually low.

I have myself seen some striking examples of the advantage of acting on Nélaton's suggestion.

I once operated for fissure of the anus on a lady above middle life, who was so exceedingly liable to fainting fits that two medical friends of hers who were present had great dread of her taking chloroform. For my part, I believed that if she was to be operated on at all, chloroform would prove advantageous by protecting her heart from shock. It was accordingly administered, and she took it perfectly well; but before she was fully under its influence I yielded to the entreaties of my colleagues, and against my own judgement proceeded to the operation. As the knife passed through the sensitive part she ceased to breathe, and became deadly pale. I instantly turned her round across the bed, so that her head and shoulders hung over its side, and performed artificial respiration by Sylvester's method. In a short time natural breathing recurred; and when it had continued for a while, I replaced her in the horizontal position. No sooner was this done than the alarming symptoms returned; but they were again dispelled by a repetition of the same treatment. This time I took care to keep the head dependent for a considerably longer period, and the result was permanent recovery. In that case my belief was that a more complete action of the chloroform would have obviated the collapse.

In another case no such explanation of the syncope was possible.

I had performed a trifling operation upon the arm of a delicate little girl under chloroform in King's College Hospital. Nothing unusual had occurred, and she was sent off on a wheeled couch to the ward, about thirty yards distant. Whether she was made to sit up as she was lifted into bed (a thing which ought never to be done) I do not know; but she had hardly been placed there when she fell into a state of collapse, and I was at once summoned. Running to the ward, I found her face blanched, and respiratory movements entirely absent. I immediately did as in the former case. No sooner was her head placed dependent than a rosy colour suffused the white cheeks; and after a short time of artificial respiration by Sylvester's method, she was breathing naturally.

I have had occasion to refer more than once to Sylvester's method of artificial respiration. In it inspiration is effected by drawing up the arms above the head till they are in a line with the trunk, and thus raising the ribs through the medium of the muscles which connect them with the upper extremities; while expiration is produced by lowering the arms and pressing the elbows firmly against the front and sides of the chest. I can testify to the great superiority of this method over the old plan of merely compressing the thorax intermittingly, and trusting to its expansile elasticity for inspiration.

Inhalation of the vapour of a few drops of nitrite of amyl as a cardiac stimulant is stated to have proved useful in some cases of collapse under chloroform. And in accordance with the exaggerated idea of the sedative influence of chloroform upon the heart to which I have above referred, the admixture of a small quantity of the nitrite of amyl with it has been suggested as a preventive of cardiac depression. The proposal has not, however, met with acceptance; nor is it likely to do so, seeing that the nitrite, while a very potent agent, seems to be inconstant in its operation.

The same dread of the depressing effect of chloroform upon the heart has led some surgeons to use it mixed with ether, together with some alcohol to produce complete blending of the two liquids. Deaths have, however, occurred under the use of such mixtures, and we have no evidence that they are really safer than undiluted chloroform carefully given.

The hypodermic injection of morphia a short time before chloroform is administered has been recommended in Germany for some special operations, on account of the remarkable result, which certainly follows such practice, that the patient may be deprived of sensibility to pain, though still retaining consciousness and voluntary motion; so that he is able to assist the surgeon by his own exertions. I understand, however, that a very serious depressing influence upon the nervous system has been sometimes found to result from this combination of the two narcotics.

A favourite method with some London practitioners is to begin by giving nitrous oxide, and when anaesthesia has been rapidly produced in this way, maintain it by means of ether. The patient is thus saved the discomfort of the inhalation of ether, and I am not aware that any disadvantage attends the preliminary use of the nitrous oxide, except the inconvenience of the necessary apparatus, which practically must restrict this mode of procedure to dentists and persons who devote themselves specially to the administration of anaesthetics.

Ethidene dichloride, or ethidene, as it is often called for the sake of brevity, was recommended, as we have seen, by the Committee of the British Medical Association. It happens, however, that in the trials which it has received on the human subject, fatal results have been proportionally more frequent than with chloroform.

Bichloride of methylene, administered by means of Junker's inhaler, has proved itself an excellent anaesthetic. We have, however, no proof of its superiority over chloroform, either in safety of administration or immunity from subsequent inconvenience. And it has the disadvantage compared with chloroform, that it is an unstable compound when kept in contact with the air.

EFFECTS OF THE POSITION OF A PART ON THE CIRCULATION THROUGH IT

Read before the Harveian Society of London.[1]

[*British Medical Journal*, 1879, vol. i, p. 923.]

Mr. President and Gentlemen.—Having been honoured by a request from the Council that I would make some communication to this Society, I have thought that no subject could be more appropriately brought before an association connected with the name of Harvey than some observations begun several years ago, but hitherto unpublished, regarding the effects of the position of a part upon the circulation through it.

My attention was first directed to this subject fifteen years since, when I was engaged in endeavouring to devise a satisfactory method of excising the entire articular apparatus of the wrist for the cure of carious disease. In that operation, although no large arterial branches are divided, the very protracted character of the procedure would render the oozing from small vessels a source of serious loss of blood to the patient if it were allowed to go on unchecked. Accordingly, I was led to deviate from what was then the ordinary practice of restricting the use of the tourniquet to amputation, and employed the instrument in the excision referred to. And I found that, when the hand was raised to the utmost degree, and kept so for a few minutes, and then, while the elevated position was still maintained, a common tourniquet was applied to the arm, being screwed up as rapidly as possible, so as to arrest all circulation in the limb and at the same time avoid venous turgescence, I had a practically bloodless part to operate upon, and thus gained the double advantage of avoiding haemorrhage and inspecting precisely the parts with which I was dealing. And, having found such great benefit from this bloodless method of operating in the instance referred to, I extended it to other operations on the limbs.

In 1873, I was one day illustrating this subject to my clinical class in Edinburgh by raising one of my hands to the utmost while the other was kept dependent, in order to exhibit the contrast between them in redness, when a sensation of chilliness coming on in the hand that was raised made me feel, and at once express, the conviction that something more was occurring than

[1] The paper, as now published, embraces some considerations on which I did not enter at the time of its delivery, and also some facts subsequently ascertained.

could be explained by the mere mechanical effect of the position of the part upon the blood in the vessels, and that the diminution of pressure upon their walls resulting from the action of gravity upon their contained blood must operate as a stimulus to the vaso-motor nervous apparatus of the limb, so as to induce reflex contraction of its arteries.

I will now ask this man (with his arms bare) to raise one hand high into the air, while the other hangs beside him. You observe at once the striking contrast between the two. In the one elevated, not only have the veins entirely collapsed, but the colour is almost that of the limb of a corpse. So white is the hand as to imply that the minute arteries must surely be in the same state of extreme constriction as occurs during syncope.

I will now apply to the arm close to the axilla a bandage of elastic webbing, putting on the first few turns with firmness and rapidity, so as to avoid any intermediate condition of engorgement through obstruction of the return by the veins before the arteries are completely compressed; while the later turns may be put on, if we please, more leisurely and with less firmness, to ensure, by the accumulation of the elastic force, complete maintenance of such constriction of the limb as prevents all circulation. The elastic band having been fixed with a pin, the limb is lowered and the man will stand aside for a few minutes.

I may state that, when Esmarch published his method of bloodless operating—consisting, as my hearers are all aware, of first expelling the blood from the limb by means of an elastic bandage wound firmly round it from the distal extremity upwards, and then applying another elastic constricting band in the manner you have witnessed just above the first, so as to prevent recurrence of circulation on the removal of the latter—I thankfully adopted the use of the upper constricting band in preference to the common tourniquet. I did so because the elastic band has the great superiority over the inelastic strap of the tourniquet, that it follows up any yielding that may occur in the soft parts subsequently to its application, and thus prevents the necessity which we often used to find with the common tourniquet, especially if the limb was swollen through inflammatory or oedematous effusion, of tightening up the instrument repeatedly in consequence of recurrence of bleeding, attended on each occasion with venous engorgement. But, while I gratefully accepted this part of Professor Esmarch's procedure, I did not see sufficient reason for substituting his mode of emptying the limb of blood by elastic bandaging for our former practice of trusting to the elevated position. I shall recur to this point in the sequel.

Being desirous of testing with greater precision than was possible upon the human subject the correctness of the view which I had been led to entertain of the cause of the paleness of an elevated limb, I performed on November 29, 1873, the following experiment upon a horse. An arrangement having been made by means of ropes and pulleys, one rope being connected with a broad sling beneath the abdomen and others with the feet, so that the animal could be either raised into the air with the feet dependent, or laid on its side on the ground with the legs extended horizontally, or again placed on its back with the feet drawn vertically upwards, chloroform being administered, I exposed, at the lower part of one of the fore-legs, an artery about as large as the human vertebral, situated along the outer aspect of the metacarpal bone.

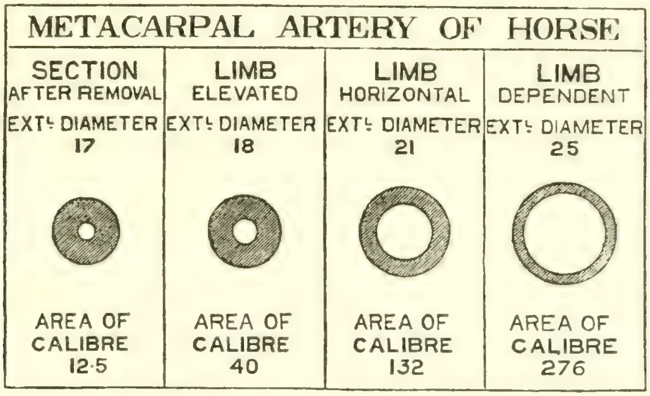
In the elevated position of the limb, the wound proved almost absolutely bloodless, closely resembling one in a dead animal ; and the artery was straight and pallid, and no pulsation could be perceived in it. When the animal was turned round so that the feet were dependent, the artery became much increased in size, tortuous, red, and pulsating powerfully, and blood oozed freely from the surface of the wound ; and when the limbs were placed horizontally, an intermediate condition took place, both as regards the artery and the haemorrhage. By means of suitable callipers, careful measurements were taken repeatedly of the external diameter of the vessel in the different positions of the animal, which, having had no chloroform administered after the conclusion of the cutting operation, appeared to be in a normal state as regards the force of the circulation. The accompanying diagram exhibits the results obtained, and also the section of the artery after removal from the body, when it was found contracted to almost complete obliteration of calibre.

You observe that, in the elevated position of the limb, the vessel was nearly as small as it was in the state of extreme constriction. On the other hand, in the horizontal, and still more in the dependent posture, the external diameter became considerably increased. But, in order to judge of the augmentation of the capacity of the tube for transmitting the blood, we must look to the area of the internal calibre, which, having measured the thickness of the wall of the artery after removal from the body, we have the means of estimating for the various positions of the limb. For, the substance composing the arterial wall being of course a constant quantity, the ring constituted by its transverse section has always the same area, though varying in form, being thinned out as the vessel expands. The area of the ring is calculated from the dimensions obtained after removal of the artery from the body, viz. the external diameter and the thickness of the wall ; and the area of the internal calibre for any other condition of external diameter is simply the area of the corresponding circle minus the area of the ring.[1] The numbers in the diagram are hundredths of an inch, and the

[1] In truth, the increase of internal calibre in the dependent position is thus rather underestimated because the tortuous form which the vessel then assumed implied a certain amount of increase in its

drawings are accurate to scale, though magnified for convenience of representation ; and from these as well as from the calculated numbers, it will be seen that, when the limb was horizontal, the area of the internal calibre was more than three times as great as in the elevated position, and that, when it was dependent, the capacity of the tube was increased about sevenfold.

The more we consider these facts, the more clear is it that they cannot be accounted for as merely mechanical results of diminution and increase of the pressure of the blood upon the arterial walls, in consequence of the different effects of gravity upon the fluid in the tubes in different positions. The arteries,



in any given state of contraction of their transversely arranged muscular fibres, are by no means disposed to yield readily in the lateral direction to increase, of pressure from within. This is evident from the fact that they are not increased in diameter by the successive strokes of the powerful muscular pump, the heart. The surgeon, when tying a large arterial trunk in its continuity, does not find, on clearing the vessel of its sheath with the point of his knife, that he is dealing with a body that swells at every pulse, but with one of unvarying dimensions. And, in the experiment on the metacarpal artery of the horse above referred to, no changes in the transverse measurements were noticed so long as the limb was maintained in any one position.[1] If any increase do occur

length ; so that the material composing its wall was thinned out, not only in consequence of lateral expansion, but also to some slight degree through longitudinal stretching.

[1] Professor A. W. Volkmann, in his valuable work, *Die Haemodynamik*, relates experiments which he made by forcibly injecting water into portions of arteries removed from the body, proving that they yielded in the transverse direction even more than in the longitudinal to pressure from within. But Volkmann wrote before the discovery of the vaso-motor nervous system (he published in 1850), otherwise he would have been well aware that his experiments on dead animals left out of account altogether the most important element in this question, viz. the muscular contraction of the vessels as distinguished from mere elasticity. Volkmann admits that, when an artery is laid bare in the living animal, the only perceptible evidence of expansion of the vessel during pulsation is the tortuous form assumed by it at every pulse in consequence of longitudinal stretching, and that the transverse distension which he supposes to take place on theoretical grounds is inappreciable. Even in the dead vessel, he could

in the diameter of an artery in systole, it is inappreciable by ordinary methods of measurement.

Yet, the increase produced in the pressure of the blood upon the arterial walls by the ventricular contractions is certainly very great. When the coronary artery of the lip is divided in a child in the operation for hare-lip, the little fountain of blood that springs from the cut vessel may be sometimes seen to rise about twice as high in systole as in diastole, implying that even in so small a branch, in spite of the equalizing tendency of the elasticity of the tubes of transmission, the systolic pressure of the blood is double the diastolic.

The tracings given by the recording haemodynamometer, and reproduced in modern physiological works to illustrate the variations of the blood-pressure, though very interesting in some respects, are entirely untrustworthy as indications of the relative pressures of systole and diastole. For, in all such instruments, the apparatus opposes more or less resistance to the altering pressure, and time is required to overcome that resistance, so that rapid variations, such as those of the cardiac pulsations, are most inadequately represented.

With reference to the present inquiry, I was anxious to obtain definite information on this important point ; and it occurred to me that this might be simply and surely done by making the blood write its own record, by means of a stream issuing from a minute orifice in a tube tied into an artery, the projected blood being allowed to fall upon a horizontal sheet of paper drawn smoothly past the animal. By such an arrangement, the effects of the varying degrees of pressure of the blood would be observed untrammelled by any resisting apparatus ; and, as the range of projection is directly proportioned to the projecting force, a comparison of the distance to which the blood was thrown

not obtain evidence of transverse yielding by measurement with the compasses, but only by calculation from the observed increase in length which the vessel experienced when over-distended with liquid, together with the increase in the volume of the tube, as indicated by the additional weight of water which it admitted, vide op. cit., pp. 407, 422, and 423. The impressions conveyed to the finger in feeling the pulse, and also the indications of the sphygmograph, are no evidence of expansion in the cylindrical tube. In both cases, pressure is made upon it, producing a more or less oval condition of the transverse section of the vessel ; and the impulse experienced is essentially the result of a tendency to restoration to the circular form as the blood-waves pass through the constricted part. A precisely similar pulse is produced in a cylindrical tube of inelastic but flexible material, through which a fluid is forcibly driven in a jerking stream. In an actual experiment made to illustrate this point, the inelastic tube was formed of a strip of thin macintosh cloth, with its edges stitched closely together. One end of this tube was connected with a piece of caoutchouc tubing, through which water was driven by a force-pump, while the other end of the inelastic tube was continued in another piece of caoutchouc tubing, the distal end of which had a somewhat narrow glass tube tied into it to simulate the resistance in the capillaries, and ensure a continuous though jerking stream by bringing into play the elasticity of the caoutchouc and of the air in the air-chamber of the pump. At every stroke of the pump, the finger, placed on the inelastic tube of macintosh, experienced a sensation exactly similar to that in feeling the pulse. When the pulse is visible in the human subject, the appearance is unquestionably caused by the movements of the vessel, as it becomes alternately curved and straightened in systole and diastole.

in systole with the distance in diastole, as indicated by the curve formed by the drops sprinkled on the paper, would afford perfectly trustworthy evidence of the relative amounts of systolic and diastolic pressure. In an experiment of this kind performed upon a dog under chloroform, but with the circulation very active, a curved glass tube being tied into the external carotid, with an orifice only ·0075 of an inch, so small in proportion to the calibre of the common carotid that the outlet could not materially affect the blood-pressure, the stream which issued from the tube, inclined at an angle of about 45 degrees, was projected twice as far in systole as in diastole. And very similar results were obtained with a tube tied into the common carotid of a rabbit operated on without anaesthesia.[1] We are, therefore, not far wrong in considering the pressure of the blood upon the walls of a considerable artery as doubled, in normal circulation, through the contraction of the ventricle.[2]

Now, we have no reason to suppose that the elevation of the leg of a horse from the horizontal to the vertical position, or vice versa, would produce a greater difference than this in the pressure of the blood upon the arterial walls. The original manometrical experiment of Stephen Hales, though performed with comparatively rude apparatus, is strikingly illustrative of this point. Having tied into the femoral artery of a horse a brass tube adapted to a long one of glass held in the vertical position, he found that the blood rose in the glass tube to the

[1] Dr. Burdon-Sanderson has pointed out to me that I have not been the first to make the blood-stream write its own record upon paper. In 1874, which is before the date of the experiments mentioned in the text, Dr. Leonard Landois of Greifswald published, in Pflüger's *Archives for Physiology*, an account of what he terms Hämautographie, and gave photographic representations of tracings obtained by drawing a piece of paper past an animal in which he had opened an artery, so that the stream of blood was received upon the paper. These tracings are very beautiful, especially from the light they throw upon the phenomenon of dicrotism of the pulse and the respiratory curve, but they were not designed to estimate the relative force of systolic and diastolic pressure, and no inference can be drawn from them with reference to that question. Instead of having a tube tied into the artery with an orifice so small as to have no appreciable effect upon the tension of the blood in the vessel, as in my experiments, the stream was allowed to flow from the divided artery either directly or through a tube of uniform calibre inserted into it to prevent closure of the orifice; and instead of having the paper placed horizontally at a given distance from the artery, to show the range of projection, he held it perpendicularly to the stream, and no mention is made of its distance from the vessel.

[2] It may perhaps be objected, that the results of the experiments described in the text cannot be taken as a fair indication of the increased pressure upon the arterial walls in systole, because, in the actual circulation, motion of the blood is produced as well as tension, whereas these two effects are confused together in the experiments, inasmuch as the stream which issues from a tube tied into an artery is the result of the entire force of the heart. This would be a valid objection if the actual amount of the tension upon the vascular parietes were the object of inquiry, but it has no force whatever against an estimate of the relative amounts of the systolic and diastolic pressure; or, to speak more strictly, the increase of tension in systole is underestimated by the method of experimenting; because, when fluid is injected through a tube offering a certain amount of resistance to its passage (as is the case in the vascular system), an increase of the force with which the liquid is injected produces less proportionate increase of motion than it does of tension; and, therefore, a method of experimenting which represents the effects of the entire force of the circulation, without distinguishing between motion and tension, underrates the increase of tension at the higher pressures.

height of 9 ft. 8 in. above the level of the left ventricle,[1] whereas the distance from the level of the heart to that of the metacarpal artery, where I operated, is only about four feet. That is to say, the column of blood from the level of the heart to that of the artery, when the limb was raised, had not half the height of that which the force of the heart was able to sustain in one of the main arterial trunks. Now we know that the pressure of the blood is not materially less in arteries of secondary dimensions, like the metacarpal, than in the main trunks.[2] And therefore the raising of the limb into the vertical position could not, as the mere result of the action of gravity upon the blood, diminish the pressure of the fluid upon the arterial wall by as much as one half ; or, conversely, the putting the limb down again could not do so much as double the pressure of the blood upon the vessel.

Seeing, then, that the doubling of the pressure which results from the contraction of the ventricle has no appreciable effect upon the diameter of an artery, it appears clear that the great alterations in the size of the metacarpal artery of the horse which resulted from varying the positions of the limb cannot be explained on mere hydrostatic principles, and that, in order to account for them, we must admit contractions and relaxations of the muscular coat of the arteries in obedience to nervous action.

That the force of the heart is amply adequate in the human subject to drive the blood freely through the vessels of the distal parts of a limb, in spite of the elevated position, provided that the arteries are relaxed, I shall now have the means of plainly demonstrating. The constricting band has been on this man's arm for eight minutes, yet, thanks to its efficacy as a tourniquet, the limb remains as pale and corpse-like as when the application was made, although he has kept his hand down in the interval. I shall now ask him to raise the hand again to the utmost degree ; and, while it is so placed, I shall remove the elastic bandage. This having been done, you observe that the skin of the hand is beginning to show patches of redness, and now, a few seconds more having elapsed, even the finger-tips, as well as the rest of the limb, are of florid red hue. The

[1] See *Statical Essays*. By Stephen Hales, D.D., F.R.S. 1769.

[2] Poiseuille, the inventor of the mercurial haemodynamometer, believed, as the result of his experiments, that there was no appreciable difference in blood-pressure between vessels of much greater divergence in size. Thus, in one of his experiments (see Poiseuille, *Recherches sur la Force du Cœur*, &c., 1828, p. 36), he found that the mercury rose to the same height in the haemodynamometer in the carotid of a horse as in a muscular branch of the femoral only two milimetres in diameter, whereas the metacarpal artery on which I operated had fully two and a half times that dimension. Marey, indeed, states (*Circulation du Sang*, 1863, p. 150) that the mean tension of the arteries decreases as the vessel is situated further from the heart, and as its calibre diminishes. But, though this is no doubt strictly true, yet it is allowed by physiologists that ' the fall ' in pressure ' is a very gradual one until the smallest arteries are reached ' (Michael Foster, *A Text-book of Physiology*, second edition, 1878, p. 102).

veins, you see, remain collapsed, the blood being continually drained out of them by the action of gravity ; but the arteries, in spite of that action, instead of being empty or nearly so, as they were when the limb was previously elevated, are distended even to the remotest capillaries. He will now raise the other hand, and you observe the extraordinary contrast between the two limbs, both in the elevated position, the hand last raised becoming as pallid as the other did before the elastic band was applied.

It is worth while to consider shortly how it is that the constricting bandage gives rise to arterial relaxation. It is well known that troublesome after-bleeding not unfrequently follows the application of Esmarch's bloodless method. This is commonly attributed to a temporary paralysis of the vaso-motor nerves, in consequence of the pressure to which they have been subjected. Now, in the experiment which you have just witnessed, one of the two factors in Esmarch's method which might be supposed to have such an effect—viz. the tight elastic bandage, applied from the distal extremity upwards, and temporarily compressing the branches as well as the trunks of the nerves—is absent ; so that we have merely to consider the effect of the constricting band upon the nervous trunks at the root of the limb. It is no doubt true that in the arm, where the soft parts are in small proportion to the cylindrical bone, if, instead of an elastic bandage, an india-rubber tube be employed as the constricting agent, in accordance with Esmarch's original proposal, the concentrated pressure so exerted may, in case of a protracted operation, lead to paralysis of a very troublesome if not serious character, both of motion and sensation. But if we follow Esmarch's more recent advice, and diffuse the pressure by using the broad bandage, no such effects are observed. I have tried the experiment upon myself, and I have found that the bandage, applied sufficiently firmly to arrest all circulation and sufficiently long to produce the after-blush in the raised limb, did not affect in the slightest degree either the sensation of my hand or the motor power of the forearm. And as there is no reason whatever for believing that the vaso-motor fibres in the trunks of the nerves are more likely to suffer from compression of those trunks than the sensory and voluntary motor fibres, the theory of paralysis from compression falls to the ground. That which seems to me to be probably the true explanation is, that when a part has been deprived for a while of circulation, the want of the vital fluid creates in the tissues a demand for a supply of it, and that this demand operates upon the vaso-motor nervous apparatus of the limb as a stimulus inducing arterial relaxation, in a manner perhaps analogous to that in which the 'besoin de respirer', as the French have termed it, produces a stimulus to the respiratory nervous system. We know that in the case of the arteries different stimuli produce different effects ;

cold inducing reflex arterial contraction, while heat occasions, equally through the nervous system, a relaxation. According to this view, then, the necessity for circulation, if I may so express myself, is a stimulus to dilatation which, when sufficiently urgent, overpowers the stimulus to contraction occasioned by the diminution of pressure upon the vessels in the elevated position. And, as a matter of fact, we find that the after-blush is greater the longer the time during which circulation has been arrested, although without anything to indicate nervous paralysis. In complete harmony with this view are the phenomena observed in a limb after ligature of its main artery. When the femoral is tied for popliteal aneurysm, the first effect upon the foot is pallor and coolness ; but, after the lapse of some hours, the converse condition of abnormal redness and heat supervenes. Here there is certainly no interference with the nerves, but the usual supply of blood is in the first instance notably diminished ; and, as a consequence of this, long before there has been any possibility of organic increase in the vessels, the anastomosing branches become so much dilated as to more than compensate for the obstruction of the principal source of supply. This effect can only be brought about through the nervous system ; and the most natural explanation seems to be that deficient circulation in a part continued for a considerable time comes to operate as a stimulus to arterial relaxation.

I have now to mention an experiment which any one may easily perform upon himself, but which, though extremely simple, is not on that account the less instructive. But first let me state the considerations that led me to it. If the contraction of the arteries of an elevated limb were really the result of an action of a particular part of the nervous system, it might be expected that, on the cessation of the stimulus that evoked it, an unusual relaxation would ensue, corresponding with a period of repose of the nervous apparatus concerned ; and that this would be more marked the greater and more protracted had been the effort. Supposing, then, that the hand were raised after the circulation had been brought into full activity by brisk exercise, with the heart working powerfully and the arteries generally in a state of considerable dilatation, if, in spite of these unusual obstacles to arterial contraction, pallor of the limb should result from the elevated position, it might be anticipated that, when the hand was again lowered, it would not only resume its former redness, but acquire for a while a deeper tint than the other, which had been kept dependent throughout. My first trial of this kind was made just after I had been walking with great haste to catch a train, when my heart was beating with unusual vigour, and my hands were of florid colour. Having raised my left hand, I saw it become, within half a minute, very pale, and on putting it down after it had been a minute in that position, I observed it grow, within a quarter of a minute, much deeper in arterially red tint than the right, a difference which gradually passed off, so that, in the course of one minute and three-quarters, the hands were again of equal colour. Two minutes later, I repeated the experiment, and this time kept the left hand raised for two minutes, and then, on lowering it, found it to become in ten seconds much redder than the other, which had been suspended the whole time ; and, just as might have been expected after the more protracted action of the nervous apparatus, the repose was longer in duration, so that, even after two minutes and twenty seconds, when I was obliged to start for the train, the left hand was still slightly the redder of the two. Now such a result as this was entirely contrary to what could be explained as a consequence of mere hydrostatic laws. If the arteries had been simply emptied in the elevated position by the force of gravity, all that could have resulted on restoring the limb to the dependent posture would have been a return more or less rapidly to the previous condition of vascular fullness. And it is an interesting fact that the veins, though comparatively thin-walled, and much more readily distensible than the arteries, do not at once recover their former size when the elevated limb is lowered, but remain for a while markedly less turgid than those of the other hand, even when, through arterial dilatation the colour of the skin is not only more florid but manifestly darker. Hence this apparently trivial experiment, if duly considered, seems to me of itself sufficient to prove the truth of the doctrine for which I am contending.

ON THE APPLICATION OF A KNOWLEDGE OF HYDROSTATICS AND HYDRAULICS TO PRACTICAL MEDICINE [1]

Abstract of an Address delivered before the Medical Society of University College, London on October 11, 1882.

[*Lancet*, 1882, vol. ii, p. 638.]

Referring to Mr. Beck's remark, in his excellent introductory lecture,[2] that physiology is the application of chemistry and physics to the study of life, Mr. Lister said that it would naturally be expected that physics would be one of the subjects in which medical students would be compelled to show a certain amount of proficiency. By the latest regulations of the Medical Council students could be registered without giving evidence of any knowledge of physics, and as this subject was not required by the Royal College of Surgeons, these students could, and no doubt would, become registered practitioners without such training. In view of this, he proposed to show some of the practical uses in medicine of a knowledge of the simple facts of hydraulics and hydrostatics.

Mr. Lister then first referred to the fact that fluid always maintains the same level in communicating tubes of different calibre, and from that passed on to describe the 'hydrostatic paradox' and the Bramah press. As a practical application of this principle he adduced the treatment of a wound of one of the palmar arches. In such a case it was necessary to enlarge the wound sufficiently to see the exact bleeding-point, and to place the apex of a graduated compress exactly on this point ; for if the compress were inaccurately applied, the blood finding its way out of the wounded artery would convert the wound into a kind of Bramah press, and either force up the compress or distend the interstices of the softer tissues. From this Mr. Lister passed on to consider some of the simpler facts about fluids in motion. For this purpose he had a vessel of coloured water raised above the table, from which depended a rubber tube connected at its end with a fine glass nozzle. Allowing the fluid to flow through this apparatus, he noted the height of the jet of water, and then replaced the middle of the tube by an equal length of tube of double the diameter and four

[1] Note by Lord Lister, April 1908 : The account of this Address here given was published without my authority, and, though fairly accurate as a condensed report, is, as was natural under the circumstances, very imperfect.

[2] *Lancet*, 1882, vol. ii, pp. 559, 607.

times the capacity, and pointed out that, the force remaining the same, the height of the fountain of fluid was practically the same. He used this experiment to show that large varicose veins do not increase the labour of the heart or impede the return of blood to the heart, and that those writers who made such statements were evidently ignorant of simple physical laws. He next held the tube at various elevations, and showed that the position of the tube did not influence the height of the fountain or the flow of blood through the tube, and therefore the effect on the blood circulation of raising or depressing a limb could not be explained on simple hydraulic principles, except in so far as the increased or diminished blood-pressure might cause distension or shrinking of the blood-vessels. And how were the facts to be explained, that raising the head of a debilitated patient may cause syncope and anaemia of the brain, and depressing the head of a fainting person will infallibly cure the faintness and restore the circulation in the brain? What was wanted was relaxation of the arteries; the mere action of gravity would tend rather to the dilatation of the veins, and as the brain is contained in a closed rigid cavity, it was impossible to explain the facts on mere hydraulic principles. Mr. Lister stated that many years ago he had a horse slung and laid bare one of the metacarpal arteries; if, now, he were held with the foot dependent the wound bled freely, and the artery was dilated and pulsated freely, while when the horse was inverted and the hoof raised in the air the wound ceased to bleed, and the artery contracted and ceased to pulsate visibly; in the horizontal position the condition was intermediate. Stephen Hales, who was a vivisector, though a divine, had shown that the blood-pressure in the carotid of a horse raised a column of blood seven feet high, and it was clear, therefore, that the effect in Mr. Lister's experiment was not due simply to the action of gravity. Further, when a large artery, such as the femoral, is exposed for the purpose of applying a ligature around it, the vessel is seen to be of a constant size; the pulse does not affect its calibre even when it is measured accurately by calipers; the vessel becomes slightly elongated, but the circular muscular fibres do not permit of lateral yielding of the vessel to any degree, and yet the blood is altered enormously during the cardiac systole. In reference to this, Mr. Lister warned his hearers against being misled by certain pulse-tracings in physiological works, in which the effects of respiration on the pulse were shown by large curves, and that of the cardiac systole by only short notches in the line, as if the effect of respiration on the arterial pressure was much greater than that of the heart. The explanation was that the effect of the heart's contraction took some time to show itself, and before it was fully recorded by the apparatus it was interrupted by the diastole. He had himself, many years ago, performed the following experiment :—Tying into the external carotid artery of a dog a glass tube with an aperture less than one-hundredth of an inch in diameter (so that the loss of blood should be insignificant), he directed the fine fountain of blood on to a sheet of white paper, which was regularly moved along ; in this way a tracing was made by the blood itself, which showed that the arterial pressure during the systole was double that during diastole.

From these facts it is evident that we must look to the vaso-motor system to explain the cause and cure of a fainting-fit by position of the head, and the effects of position upon the blood-flow. When a limb is raised, blood flows down by gravity and the veins are relaxed, and we can imagine that an afferent stimulus is thus excited which, reflected along the vaso-motor nerves, contracts the arteries. If, however, the tissues are kept for a long time ill supplied with blood, there is such a demand set up for this fluid that the vessels dilate even in spite of the elevated position of the limb, which originally caused anaemia. This was illustrated by the well-known experiment of keeping one arm raised above the head and the other dependent, the former becoming pale and the latter turgid. An elastic band was then rapidly wound round the upper part of the elevated arm, and when, after a few minutes, this was removed, the whole limb became suffused and redder than its dependent fellow. Illustrations of the working of this principle were to be seen in the sequence to the ligature of a large artery, the limb at first becoming cold and pale from mechanical cutting off of the blood-supply, and then hot and suffused from dilatation of the vessels as a result of tissue-starvation. For the same reason, in piles and affections of the pelvic viscera raising the lower limbs gave great relief, for the contraction of the arteries was not limited to the limbs, but spread to the vessels of the pelvis. As a further instance, he mentioned the case of a man who suffered extreme pain in his testicles when in an upright position, but was immediately relieved by sitting down and putting up his feet. Raising the arms above the head too was a well-known means of stopping epistaxis, and succeeded, because the contraction of the arteries of the arms spread by sympathy to those of the Schneiderian mucous membrane. Mr. Lister concluded by stating that he hoped that the few illustrations he had been able to give would show the value of a knowledge of hydrostatics and hydraulics, especially as indicating where physiological effects were produced by other than physical causes.

ON THE COAGULATION OF THE BLOOD IN ITS PRACTICAL ASPECTS

The Annual Oration to the Medical Society of London, delivered May 4, 1891.

[*British Medical Journal*, 1891, vol. i, p. 105.]

MR. PRESIDENT AND GENTLEMEN.—Thirty years ago, Dr. Alexander Schmidt, of Dorpat, enunciated a totally new view of the coagulation of the blood. Having rediscovered the fact observed many years before by Dr. Andrew Buchanan, of Glasgow,[1] that hydrocele fluid—uncoagulable in itself—is made to coagulate by the addition to it of the serum of blood already coagulated, and pursuing extended researches in the line thus indicated, he came to the conclusion that fibrine does not exist as such in solution in the plasma, but is composed of two albuminoid substances, one present in the liquor sanguinis, to which he gave the name of fibrinogen, and the other a constituent of the blood-corpuscles, and this he termed the fibrinoplastic substance.[2]

It might be objected to Professor Schmidt that the hydrocele fluid and the various dropsical effusions with which he had worked were not fairly comparable to liquor sanguinis; that they were transudations through the walls of vessels, and that the liquor sanguinis might have become in one way or another altered in the process of transudation. This objection was, as I believe, removed by an observation made by myself about the same period.[3] It had fallen to my lot to observe that in mammalia, whereas the blood usually coagulates soon after death in the heart and the main vascular trunks, in the secondary vessels it remains fluid for an indefinite period, and that not only in those of small calibre, but, if the animal be large, in large vessels also. This being understood, I proceeded as follows: Having removed a portion of the jugular vein of a horse with the blood contained in it, between two ligatures, I suspended this segment of the vein in a vertical position. In the blood of the horse, the red corpuscles behave in a totally different manner as regards their aggregation from those of a healthy man or of the ox. In the horse, instead of the red corpuscles

[1] *Proceedings of the Glasgow Philosophical Society*, February 19, 1845.

[2] *Archiv für Anat. Phys.*, &c., 1861 and 1862.

[3] The Croonian Lecture, by the author, 'On the Coagulation of the Blood,' *Proceedings of the Royal Society*, 1863, p. 606 (page 109 of this volume).

assuming the condition of a delicate network of rouleaux, they become aggregated into dense spherical masses, often visible to the naked eye, like coarse grains of sand ; and these densely aggregated corpuscles, falling more quickly than the rouleaux in the liquor sanguinis, as hailstones fall more rapidly than snow-flakes, soon leave the upper part of the fluid comparatively free from corpuscles ; so that within about half an hour the upper third, or it may be half, of the blood is a transparent liquid.[1] When I had ascertained through the translucent walls of the vein that this state of things had occurred, I punctured the upper part of the vessel, so as to let out some of the clear fluid, and found that it was very slow in coagulating. In about three-quarters of an hour it had only begun to coagulate, whereas a little of this same clear fluid, to which a small portion of coagulated blood was added, clotted in a very short period. That the clear fluid did coagulate at all was sufficiently explained by microscopical examination, which showed that there were present in it some red corpuscles and numerous white corpuscles. It was obvious that if we could have separated the corpuscles absolutely from the liquor sanguinis, there would have been no coagulation at all ; and as the separation of the corpuscles from the plasma had occurred, not by transudation through vascular walls but simply as the result of gravity, it could be no longer doubted that Schmidt's conclusions were essentially right.

During the time that has since elapsed various endeavours have been made to ascertain the precise nature and mutual relations of the constituents of the liquor sanguinis and the corpuscles thus concerned in the formation of the fibrine. This inquiry cannot be said to be yet terminated, and it is, at the present time, uncertain whether Schmidt's simple original view may not be correct, that there are two albuminoid substances, one in the plasma and one in the corpuscles, which combine to constitute fibrine.

These investigations, most valuable as they are, have, as it seems to me, somewhat overshadowed the question, which is after all the most interesting to us as practitioners, namely, What are the circumstances that determine the mutual reaction of these two constituents ? What are the conditions under which the corpuscles are induced to give up their element of the fibrine, to combine with the element in the liquor sanguinis ? This subject engaged a large share of my attention many years ago ; and, though I am afraid I have not much of novelty to communicate regarding it, yet in consequence of its very great impor-

[1] The same thing is seen in the mixture of serum and corpuscles obtained by stirring the blood during coagulation. In that from the horse the red corpuscles subside from about the upper third of the liquid within half an hour ; whereas that from the ox shows only a thin layer of serum after the lapse of twenty-four hours. I am surprised to see that in some textbooks the buffy coat is attributed to slowness of coagulation.

tance, I have thought that it might perhaps be not unworthy of the circumstances in which the kindness of your Council has placed me this evening.

Shortly before my investigations began, Professor Brücke, of Vienna, had conducted an inquiry into the conditions which determine coagulation, and had arrived at conclusions which to a certain extent resembled those to which I was led.[1] He found, as I also did, that there is a world-wide difference, in their relations towards the blood, between the walls of the living vessels and ordinary solid matter ; and Brücke concluded, as Sir Astley Cooper and others had done before him, that this difference consisted in an active state of the living vessels ; that the blood-vessels, by an action which they exerted upon the blood, prevented it from coagulating. My investigations, on the other hand, led me to conclude that healthy blood has no spontaneous tendency to coagulate ; and that the walls of the blood-vessels are not active, as Brücke supposed, but passive in their relation to coagulation ; that ordinary solids induce coagulation by an attractive influence—comparable, perhaps, to that which a thread exerts in causing the deposition of sugar-candy from a solution of sugar—while the healthy living tissues differ from ordinary solids in being destitute of this attractive influence.

Out of many experiments tending to this influence, published long ago,[2] I may be permitted again to describe one which not only appears to me conclusive on the point at issue, but is also of interest otherwise. A portion of the jugular vein of an ox with the blood in it being held vertically, I cut off the upper end, taking scrupulous care that the wounded part of the vessel did not come in contact with the blood, and then passed down into the vein a tube composed of very thin glass of a calibre rather less than that of the jugular vein, its upper end being stopped by a perforated cork in which was inserted a narrow glass tube, which again was continued with a short piece of vulcanized india-rubber tubing. The tube was pressed with the utmost steadiness down into the vein, so as to disturb the blood as little as possible. In the course of time, the vein being a little squeezed, blood made its appearance in the narrow glass tube, and then at the end of the india-rubber tube. When this was the case, the india-rubber tube was secured by a clamp, and the whole apparatus was rapidly inverted, and the piece of vein withdrawn. Waterproof tissue was then tied over the open end of the large tube to prevent evaporation and exclude dust, and the tube was securely fixed and left undisturbed. Thus we had blood present in a vessel consisting entirely of ordinary solid matter, but having been subjected in a minimum degree to the influence of the ordinary solid : and the result was that when I came to examine the blood after the lapse of ten hours, I found it

[1] *British and Foreign Medical Review*, 1857.

[2] The Croonian Lecture, *Proceedings of the Royal Society*, loc. cit.

still fluid, with the exception of a crust of clot lining the wall of the vessel. This, gentlemen, seemed to me of itself to afford sufficient evidence that healthy blood has no spontaneous tendency to coagulate, requiring to be kept in check by an action on the part of the walls of the living vessels. This blood had been entirely withdrawn from the vein, and yet it remained fluid except where in contact with the ordinary solid.

This conclusion has been comparatively lately strikingly confirmed by the experiments of more than one observer. I would especially allude to one performed by Professor Berry Haycraft.[1] He has found that if a drop of blood is introduced, under suitable precautions, into a deep narrow jar of castor oil, and before the drop, which falls slowly through this oil, has reached the bottom of the vessel, the jar is inverted, and the drop made to retrace its steps without having touched the glass, this process being repeated again and again, the drop of blood, having never come in contact with an ordinary solid, remains fluid for an indefinite period. This experiment may perhaps appear to some of you even more conclusive than mine, inasmuch as no coagulation whatsoever occurs in the drop of blood under these circumstances. Certainly it seems to me that it confirms in an absolutely unmistakable manner the view to which I had been previously led.

But there is also this interesting circumstance in Professor Haycraft's observation. It had been shown amply by myself that the gases of the atmosphere are incapable of inducing coagulation of the blood ; but experiments like those of Professor Haycraft show that the same is the case with neutral or chemically indifferent *liquids*. This seems to me to be an exceedingly interesting fact, namely, that the active living tissue, such as lines the wall of a healthy vessel, in its relation to the coagulation of the blood, resembles the mobile particles of a liquid.[2] I say the *active* living tissue ; for when the living tissue becomes impaired in vital energy, it behaves towards the blood like an ordinary solid. That is the case not only when a vessel is wounded, but also when it is subjected to some influence which, without actually wounding it, is calculated to suspend or impair its vital activity. A good illustration of this is afforded by a fact which I have never before referred to, but which I have often noticed. A very valuable field for simple and instructive observations regarding the conditions that determine the coagulation of the blood was afforded by the feet of sheep, removed after the animals had been killed, the blood being retained in the vessels by a bandage applied below the part where the foot is removed

[1] *Journal of Anatomy and Physiology*, vol. xxii, p. 582.

[2] Dr. Freund, of Vienna, almost simultaneously and independently observed this relation of inert liquids to coagulation, *Jahresberichte für Anatomie und Physiologie*, 1886.

by the butcher. The blood remains fluid for days in the veins of such feet, while, at the same time, the persistent vitality of the vessels is shown by the fact that they contract when exposed by reflexion of the skin.[1] Now it happened that the butcher, in order to keep the sheep from struggling, always tied the feet together with a firm cord applied below the part where my bandage for retaining the blood was passed round ; and I invariably found the blood coagulated in the superficial veins at the part where they had been pinched between the cord and the bone. There is no reason to suppose that the temporary application of the cord had deprived the veins of their vitality at the part subjected to its pressure. If the sheep had been released, I have no doubt whatever that the veins would have remained alive. But though the vessels had not been wounded but only squeezed, only had their vital energies temporarily impaired, nevertheless the blood had coagulated in them at the part so treated. Just as by pinching a portion of the web of a frog's foot with the padded ends of a pair of dressing forceps you can induce, by the irritation of mechanical violence, an intense degree of inflammatory congestion, in which the pigment cells for the time being have their vital functions of diffusion and concentration of the pigment perfectly suspended, and yet are in a condition which is recoverable,[2] so did these veins, subjected to a similar agency, experience, though unwounded, a temporary prostration of their vital power. Thus it appears that the living tissues, which, while in a healthy active state, differ from ordinary solids in not occasioning the coagulation of the blood, themselves act like ordinary solids, and induce coagulation when their vital energies are suspended.

Another point to which my investigations were at that time directed was the behaviour of the blood-clot in relation to coagulation. I came to the conclusion that, in a healthy state of the blood, an undisturbed coagulum resembles living tissue in its behaviour with regard to coagulation ; that an undisturbed clot does not induce coagulation in its vicinity is a most important truth if it be such. This is well illustrated by the fact with regard to the sheep's foot, to which I have already referred. We have seen that, on the one hand, where the tight cord had pressed the veins, coagulation occurred in those veins, but on the other hand that the blood remained permanently fluid in other parts of the same vessels. In other words, the clot induced by the action of the cord upon the veins had not been able to spread, although the blood in the veins was perfectly at rest ; the clot could not propagate itself. The same thing is

[1] The blood in the amputated limb becomes gradually impaired in its coagulating property. A few hours after amputation it is found to clot more slowly than at first when exposed to the influence of ordinary solids, and after some days fails to coagulate at all.

[2] See a paper by the author 'On the Early Stages of Inflammation', *Phil. Trans.* Part II, for 1858, p. 682 (page 209 of this volume).

seen in any amputated limb in which the blood-vessels are sound. If such a limb is examined, say twenty-four hours after amputation, you will find that there exist clots in the vessels where they were wounded by the knife in the operation, but that elsewhere the blood remains fluid and coagulable. I came, therefore, to the conclusion that an undisturbed blood-clot is unable to induce coagulation in its vicinity ; and I think that the instances I have given demonstrate that such is really the case.

Yet in the experiment which I have described, where a glass tube was slipped down into the jugular vein, the coagulum did propagate itself. I found, as before mentioned, on examining such a tube ten hours after it had been charged with blood, that the crust of clot which lined the tube was only a thin one ; but in another experiment, nearly two days having been allowed to pass before examination, the layer of clot was thick, and there remained only a small channel in the middle of it, with the blood still fluid and coagulable. How is this difference of behaviour between the clot within the vessels and the clot outside them to be explained ? At the time when I performed the experiment, I was disposed to think that it must be due to some imperfection in the mode of performing it ; that in spite of all the care that I had taken in very steadily pressing down the very thin glass tube, nevertheless the blood must have been influenced by the glass for some considerable distance.

I am now inclined to believe that another explanation must be given. It was ascertained by Schmidt that (to adopt provisionally his original nomenclature) the fibrinoplastic substance emitted by the corpuscles is in excess of what is required in order to combine with the fibrinogen of the liquor sanguinis. This, in fact, is obvious from the fundamental truth that serum expressed from a shrinking clot, when added to hydrocele fluid, induces coagulation. The blood is coagulated already ; the fibrine is already formed in it ; and yet the serum contains fibrinoplastic substance in solution free to combine with the fibrinogen of the hydrocele fluid. Such being the case, we see that, in the experiment with the glass tube, the clot first formed under the influence of the glass, shrinking and squeezing out its serum containing fibrinoplastic substance, this must combine with the fibrinogen of the adjacent liquor sanguinis, forming fresh fibrine, and producing a new layer of coagulum.

This, however, will only account for a very limited extension of the clot ; inasmuch as the fibrinoplastic substance of the original coagulum having now all completely combined with fibrinogen, none will remain in solution, and thus the serum pressed out by the shrinking of the new layer will not contain fibrinoplastic substance, unless some new agency comes into play, to induce the corpuscles of the last-formed coagulum to give it up. Such an agency is, I suspect, present in the shrinking of the fibrine, which, as a matter of theory, seems quite as likely to have such an influence on the blood-corpuscles as the attractions of an ordinary solid. If such be the true state of the case, the clot must go on perpetuating itself indefinitely, however slowly.[1]

But how are we to explain the non-extension of the clot within the vessels in the cases referred to? How are we to explain the fact that it did not spread from the vicinity of the tight cord in the sheep's foot, and does not extend beyond the vicinity of the wound in the amputated limb? Again, why is it that the coagulum never propagates itself from the wound in the vein after phlebotomy? That wound—intentionally made somewhat gaping—is certainly, in the first instance, occupied by blood-clot. The equable flow of the venous blood does not disturb it. It is an undisturbed coagulum. But it must often happen that the clot projects more or less into the calibre of the vessel, in which case the blood, at its lee side, will lie at rest in contact with it. Yet the indefinite extension of the coagulum, which the analogy of the blood in the glass tube would lead us to anticipate, never occurs; and we reckon with confidence on the wound in the vein simply healing without interference with its calibre.

These remarkable differences between the behaviour of a coagulum in a glass tube and within the living vessels may, perhaps, have light thrown upon them by a fact which I have on a previous occasion brought before the attention of this Society. I first observed it, eighteen years ago, in an attempt that I made to obtain pure blood-serum from a horse; letting blood, with antiseptic precautions, from the carotid artery into a flask that had been purified by heating it to a very high temperature. To my great astonishment, I found that, although the blood of the horse coagulated as usual in the flask, the clot did not shrink in the least. Though I kept it for many days, yet there was not a drop of serum to be seen upon its surface, and the sides of the clot remained in contact with the wall of the flask. This was made particularly striking by the circumstance that masses of aggregated red corpuscles, resembling grains of sand, as before described, were to be seen touching the glass in the lower part of the buffy coat. This, I need hardly say, astonished me immensely; and I imagine it was the first time that a blood-clot was ever seen not to shrink and press out serum.

It seemed hardly likely that this result could be due to the destruction of micro-organisms in the flask, although the heat had been applied for that purpose.

[1] A good example of the indefinite extension of a clot outside the body is mentioned by Freund (op. cit.). He found that, while blood might be kept fluid for an indefinite period in a vessel completely coated with paraffin, if the coating was deficient at any point, coagulation took place there and spread throughout the mass.

It was suggested to me that perhaps it might arise from some physical change in the glass due to the very high temperature to which I had subjected it. It had been observed by Liebig that, whereas a supersaturated solution of sulphate of soda is, under ordinary circumstances, made to start into a crystalline mass by contact with a glass stirring rod, no such effect is produced by the rod if it is heated in the flame of a spirit lamp and allowed to cool ; a result attributed by Liebig to some temporary physical change produced in the glass by the heat. Might it be, then, that the fibrine of the clot failed to shrink in consequence of a different molecular arrangement assumed under the influence of the glass altered by heat ? That view, however, has been exploded ; because it has been proved, as illustrated by some striking experiments shown at a conversazione of the Royal Society some years ago by my colleague, Professor Thomson, that the cause of the crystallization of the supersaturated solution of sulphate of soda is not the contact with the glass as such, but the accidental presence on the glass of minute quantities of sulphates isomorphous with the sulphate of soda ; and that the effect of the heat is to drive off the water of crystallization of those salts, and make them no longer isomorphous with it, and, therefore, no longer able to induce the crystallization. And so a mystery in physics was cleared away, and made a very simple matter. Thus the suggested explanation fell to the ground.

The same absence of shrinking of the clot had been brought about by different means in the example which I exhibited to this Society nearly seven years ago.[1] A glass jar, not especially clean, had been purified by means of a solution of corrosive sublimate in 500 parts of water. Blood had been let into this jar from the jugular vein of a horse, under antiseptic precautions, forty-one days before ; and the members of the Society had the opportunity of seeing that, just as in the case of the flask subjected to a high temperature, the clot had not shrunk ; the serum had not been squeezed out of it. And although it seems unlikely that in the short time that elapses between the shedding of the blood and the commencement of shrinking of the clot under ordinary circumstances, the micro-organisms present could have had such an influence on the blood, yet when we see that two agencies so different in their nature as a high temperature and a solution of corrosive sublimate, but both powerfully germicidal, led to the same result, one is almost inclined to think that surely it must be so. No other explanation has been offered, although I know that physiologists have been much interested in the subject.

If we admit that micro-organisms are the cause of the shrinking of the clot, and that the shrinking of the clot is the cause of its extension, it follows that

[1] *British Medical Journal*, 1884, vol. ii, p. 803 (see p. 293 of volume ii of collected papers).

an undisturbed coagulum formed within the body under healthy conditions otherwise, being free from micro-organisms, will not spread. Fibrinoplastic substance exists, no doubt, in the serum in the substance of the clot. But the experiments of the late Mr. Graham showed that diffusion of liquids is an exceedingly slow process, even between a strong saline solution and water ; and it must be a very slow process indeed between two liquids so nearly allied as liquor sanguinis and serum.

Whether this explanation be correct or not, the fact remains that an undisturbed clot of healthy blood within healthy living vessels is incapable of self-propagation.[1] On the other hand, the theory which I have suggested is in harmony with the extension of clots containing microbes, as in pyaemia.

While an undisturbed clot resembles healthy and active living tissue with respect to coagulation, a disturbed and torn clot acts in this relation like wounded tissue. And as a coagulum is an easily lacerable substance, we often see coagulation induced by a blood-clot that has been disturbed. This is perhaps most strikingly seen in aneurysm. Let us take, for instance, a traumatic aneurysm. The blood escapes from the wounded artery into the surrounding tissues ; and these having been injured, the blood coagulates in contact with them. Every successive portion of blood driven in by the force of the ventricle stretches and lacerates the clot so formed. It is an injured clot, and induces coagulation in its vicinity : and the result comes to be that while, on the one hand, the force of the heart tends perpetually to distend the sac, inferior as it is in elasticity to the wall of the artery, there is on the other hand a constant tendency to deposition of fibrine upon the interior of the sac, as if the blood were ' whipped ', and thus the wall of the sac is perpetually strengthened, exhibiting a counteracting agency tending to recovery.

A beautiful converse of this state of things is presented, as it seems to me, by some cases of varicose aneurysm, such as used to be a not uncommon result of careless venesection. Here the communication with the vein was sometimes so free that the blood driven in by the heart distended the sac comparatively little, so that the aneurysm had no tendency to increase, but was merely a source of annoyance from the purring sensation caused by the arterial blood driven into the vein. And if an operation was performed on such a case, the remarkable fact was disclosed that instead of the aneurysmal sac being lined with layers

[1] As further illustrations of this important truth may be mentioned the limitation of the coagula to the immediate vicinity of the wound in the veins of a stump after amputation ; and also the fact which I have often noticed that if a varicose vein in the leg is treated by removing portions of the vessel at intervals of a few inches, the blood, though it coagulates in the immediate vicinity of the ligatures employed, remains permanently fluid in other parts of the vein.

of fibrine, it resembled in its interior an artery or a vein.[1] The force of the blood not being able to tell upon the clot and disturb it, the clot ceased to induce further coagulation, and became organized and invested with endothelium.

We see the same thing illustrated in the different behaviour of the blood-clot above and below a ligature applied upon an artery in its continuity. When such a ligature was applied in the old-fashioned way, in the shape of a silk thread, used without any antiseptic precautions, with the ends left long, it had to come away by suppuration, and there was serious danger of secondary haemorrhage. But if this did occur, it was commonly not, as might have been expected, from the cardiac side, where the seat of ligature was subjected to the full force of the ventricular contractions, but from the distal side, where the pressure was comparatively feeble. The ligature having been applied sufficiently tightly to rupture the internal and middle coats, there necessarily occurred as an immediate result a certain limited amount of coagulation upon the injured tissues. On the cardiac side, where the force of the blood driven by the heart against the obstruction told powerfully at every stroke, the clot was perpetually disturbed, and infallibly coagulation occurred up to the first considerable branch, producing a substantial resisting plug. But at the distal side, if the circumstances of the anastomosing circulation were such that there was no pulsation, there might be no extension whatever of the undisturbed primary coagulum, so that a mere trace of clot was found on pathological examination.

I have hitherto dwelt on the view first advanced by myself and now, I believe, generally accepted—that the fluidity of the blood is not due to an active operation of the living vessels. But I am far from holding the opinion that there is no part of the vascular system that actively opposes coagulation. If transfusion is practised in the ordinary manner—say by filling a syringe with blood and injecting it into the veins of the patient—the blood is subjected to the influence of an ordinary solid, which would inevitably induce coagulation within the vessels, unless there were some counteracting agency at work. It is astonishing how very short a period of contact with an ordinary solid determines the mutual reaction of the corpuscles and the liquor sanguinis. Yet no coagulation occurs as the result of such an operation. It is, I presume, in the capillary system that the correcting influence is exerted.

Again when intense inflammatory congestion is produced by the application of some irritant substance to the web of a frog's foot, we see that the corpuscles, both red and white, adhere to one another and to the walls of the vessels, and block the capillaries. Mechanical violence is one of the many irritating agencies which produce such congestion ; and from what we know of the effects of the

[1] Syme's *Principles of Surgery*, 5th edition, p. 140.

pressure of the cord upon the veins of the sheep's foot, we cannot doubt that the blood must be coagulated in the congested vessels : that between the corpuscles there must be cementing fibrine. The distinguishing characteristic of acute inflammatory exudation is of itself pretty clear evidence to this effect. The exudations in intense inflammation differ from those of dropsy by being coagulable ; hence the brawniness of tissues that are intensely inflamed, or the lymph in acute pericarditis. How can this coagulable character of the effused liquor sanguinis be explained except by supposing that the walls of the capillaries have acted for the time being like ordinary solid matter, and that, as a consequence of this behaviour of the capillaries, the corpuscles have given up to the liquor sanguinis (to use Schmidt's language) the necessary fibrinoplastic substance ? And if the exuded liquor sanguinis coagulates, we cannot doubt that the plasma which remains in the capillaries is also coagulated. Nevertheless, if the irritant has not been pushed so far as to cause the death of the part on which it has acted, the tissues in due time recover, and we see the corpuscles gradually detaching themselves from each other, to pass on into the circulation. And we may surely say that, not only do the corpuscles recover their original non-adhesive character, but the fibrine which binds them together is dissolved.

I believe, therefore, that although in the larger vessels the vascular walls are negative as regards the coagulation of the blood, in the capillary system there must be potent agencies counteracting any tendency to clotting induced by abnormal conditions, and capable even of dissolving fibrine.

PART II

PATHOLOGY AND BACTERIOLOGY

NOTES OF THE EXAMINATION OF AN EXOSTOSIS REMOVED BY MR. SYME ON OCTOBER 2, 1853, FROM THE OS HUMERI OF A YOUNG LADY AGED ABOUT TWENTY YEARS

Read to the Edinburgh Medico-Chirurgical Society, November 16, 1853.

[*Monthly Journal of Medical Science*, January 1854.]

THE tumour was situated at the posterior and inner aspect of the bone, two or three inches from its upper end. Some idea of its general appearance may be gathered from Fig. 1 of the accompanying woodcut (see next page), which gives a lateral view of it of the natural size. It is seen to be of irregular form, presenting at its most prominent part several smooth rounded tuberosities: these were covered with cartilage, while the more circumferential parts of the tumour rose gradually from the normal level of the bone around, and were destitute of cartilage. The whole surface of the tumour was invested with extremely loose cellular tissue, which must have allowed very free gliding motion of superjacent parts; this cellular tissue adhered firmly, both to the cartilaginous and osseous portions of the surface. At *a*, a piece of the tumour had been broken off, exposing the cancellated texture of the interior, which in the deepest parts of the exostosis, was extremely loose, consisting of medullary substance traversed by very delicate spicula, which presented the microscopical characters of true bone (a lacuna with canaliculi from one of these spicula was shown in a sketch at the reading of the paper). In the circumferential parts of the tumour, which, as above stated, were destitute of cartilage, this loose cancellous structure extended to within a very short distance of the surface, which was formed by a thin layer of compact, true osseous tissue. But beneath the cartilaginous prominences there was a considerable thickness of compact substance, of a peculiar white aspect, too gritty and friable for true bone, and having a dark confused appearance under the microscope, with no definite structure; but after maceration in dilute hydrochloric acid presenting both to the naked eye, and under the microscope, the characters of cartilage. As a general rule, this calcified cartilage was present in greatest amount where the cartilage was thickest. Fig. 2 exhibits part of a section made perpendicular to the surface of one of the prominences of the exostosis; *a* is the cartilage covering the surface, and is upwards of a line in thickness; the calcified cartilage *b* immediately beneath it was very dense, while at *c* the texture was looser,

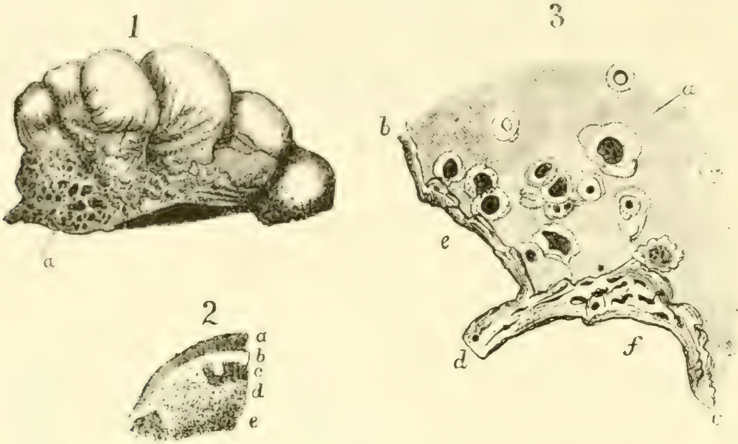


FIG. 1 is a lateral view of the exostosis: at *a* a piece of the tumour has been broken off, and the loose structure of the interior shows itself.

FIG. 2 exhibits part of a section through one of the prominences of the tumour: *a* is the superficial cartilage; *c* is a portion of cartilage situated deeply, and surrounded on all sides by dense calcified cartilage, *b* and *d*; *e* is the deepest part of the calcified cartilage, of looser texture than the more superficial parts.

FIG. 3 shows a section of a portion of the tumour at the line of junction of the calcified cartilage and the cancellous structure of the interior; the earthy matter has been removed by dilute hydrochloric acid: *a* is the cartilage with its cells changed by the process of calcification; *b c* is true bone (containing lacunae) lining the excavations in the calcified cartilage; *d* is part of a spiculum of the cancellous structure: *e* and *f* are spaces formerly occupied by medullary substance.

but even there, at a depth of five-eighths of an inch below the surface, cartilage cells showed themselves after maceration in acid.

The microscopical appearances of the superficial cartilage presented nothing very remarkable; the cells were larger than they are found in human articular cartilage, and many of them were of rather complex structure; they were much elongated at the free surface, where, indeed, it was difficult to distinguish them from the contiguous part of the investing cellular tissue; while in the deeper part of the cartilage they were more or less elongated in a direction perpendicular to the surface of calcification (a figure was shown representing one of these deeper cells). The matrix was homogeneous or faintly granular. The matrix of the calcified cartilage as seen after maceration in acid, was more granular, and the cells were rounder, and often surrounded with a broad pellucid ring, but the cells of the immediately adjacent part of the uncalcified cartilage assumed more or less of the same characters. The boundary between the uncalcified and the calcified cartilage was rendered very distinct by the circumstance that the matrix of the former was coloured brown by the action of the acid, while that of the latter generally remained colourless.

At one spot, viz. at *c* in Fig. 2, a piece of cartilage existed at a considerable depth below the general surface of calcification, and surrounded on all sides by the dense pseudo-bone; this cartilage was extremely soft, and its cells remarkably large; one of them of circular outline measured 1–285th inch in diameter; the nuclei also presented considerable variety of appearance, and complexity of structure. It might be supposed that these characters of the cells were connected with great rapidity of growth in this cartilage, and such may perhaps be the case; but the cells are not larger than exist in the central parts of costal cartilages. In the centre of a costal cartilage of a woman about sixty years old, I found cells very similar both in size and appearance, and it can hardly be supposed that any very rapid cell-development had been going on in that situation at such a period of life.

The fact that the calcified cartilage was in some places looser in texture at its deep than at its superficial parts (e.g. looser at *c* than at *b* in Fig. 2) seems to indicate a change going on in the calcified cartilage by which it becomes converted into the loose cancellous structure of the interior. Examination of the deepest parts of the calcified cartilage under a low magnifying power, after the earthy matter has been removed by acid, shows that it is invaded by processes of the medullary substance of the cancellated tissue beneath it, which advance for a variable distance into its substance, and give a very irregular eroded character to its outline. The excavations thus seen to occur in the deep border of the calcified cartilage, are often lined with a thin layer of true bone containing lacunae, which has, no doubt, been deposited subsequently to the formation of the excavations. Fig. 3 represents a small portion in this condition, where *a* is the deepest part of the calcified cartilage, *b c* is a layer of true bone lining the excavations *e* and *f*, which were formerly occupied by processes of the medullary substance; and *d* is part of one of the spicula of the cancellous structure. The true bone is distinguished from the matrix of the calcified cartilage by having a higher refractive power than it.

In the part where I first noticed this osseous lining of the calcified cartilage, it was almost universally present; very few of the excavations being even partially destitute of it. And the same appearance presented itself in the head of a metatarsal bone of a boy sixteen years of age, at the line of junction between the epiphysis and the cartilage which separated it from the shaft. Indeed, the resemblance between the two objects was exceedingly close, for the disposition of the cartilage cells in piles perpendicular to the surface of ossification, while present in the shaft of the metatarsal bone, was absent alike in the epiphysis, and in the exostosis ; also the part of the cartilage that was immediately contiguous to the newly formed bone of the epiphysis was evidently calcified, and closely resembled the calcified cartilage of the exostosis, both in the condition of the cells and in the eroded form of its margin ; the eroded edge, again, was almost universally lined with a layer of true bone exactly as in the exostosis, except that the layer was generally somewhat thicker.

These facts appeared at first inconsistent with the idea of the layer of true bone having been deposited subsequently to the formation of the excavations, for that supposition implied that both in the epiphysis and in the exostosis, the process of excavation of the calcified cartilage had almost entirely ceased, or, in other words, that the conversion of the calcified cartilage into true bone was almost or altogether suspended ; and this appeared particularly unlikely in the case of the exostosis, which was known to have been growing rapidly before its removal.

The examination of the ossifying epiphysis of one of the bones of a calf's foot has, however, convinced me that the layer of true bone is deposited on the walls of previously existing excavations. The cells of the calcified cartilage are there seen to enlarge at the expense of the matrix as they approach the cancellous structure of the epiphysis, and at the same time to acquire a granular appearance, just like that of the rudimentary medullary substance with which the last formed areolae are filled ; and finally, they evidently form by their coalescence the excavations in the margin of the calcified cartilage. Those parts of these excavations or areolae which are farthest from the perfect bone, and which have been last formed, are devoid of any osseous lining ; but at a very short distance from their extremities they acquire upon their surface a thin layer of lacunated bone, which is seen to increase gradually in thickness at the expense of the cavities as they are traced nearer to the perfect bone.

A further examination of the exostosis also showed that in some parts the osseous lining of the margin of the calcified cartilage was absent, while, on the other hand, there appeared at these parts evidence of a change in the deepest cells of the calcified cartilage, like that observed in the calf's foot, viz. an enlargement of the cells, and a conversion of their contents into a granular substance previous to their coalescence to form the excavations.

It thus appears that the process by which the calcified cartilage of the exostosis was converted into the cancellous structure of the interior, is essentially the same as what occurs in the ossification of the epiphysis of a metatarsal bone. The only difference between the two cases appears to be that in the ossifying epiphysis, the calcified cartilage is a very thin layer, while in the exostosis it is present in considerable thickness ; but even in this particular there was not a constant difference between them ; for the calcified cartilage varied much in thickness at different parts of the exostosis, and at some spots was, to the naked eye, absent or nearly so, even where cartilage existed on the surface.

The great thickness of the calcified cartilage probably results, in part at least, from a want of energy in the process by which it is converted into the cancellated tissue, and accordingly it was just at that part where the calcified cartilage was thickest (viz. at *c* in Fig. 2) that the osseous lining of the calcified cartilage was found almost universally present ; and we have seen that this condition implies an arrest in the process of conversion of calcified cartilage into cancellous structure. The languid condition of the ossific process at this part, was probably also the cause of the piece of cartilage *c* in Fig. 2 being left uncalcified below the general level of calcification.

The general conclusion to which the examination of this exostosis leads, is that it grew at the surface as cartilage, which became converted into cancellated bone by an ordinary process of ossification, in which, however, the stage of calcification of cartilage occupied an unusually conspicuous position.

REPORT OF A CASE OF CARBUNCLE

OCCURRING IN MR. SYME'S PRACTICE, ILLUSTRATING ESPECIALLY THE PATHOLOGY OF THAT DISEASE

[*Monthly Journal of Medical Science*, July 1854.]

Thomas Davidson, aet. 52, admitted into the Royal Infirmary, February 9, 1854, a weaver, residing at Sinclairton near Kirkcaldy. States that he has generally enjoyed good health, and that three weeks before his admission he was in no respect worse than usual; he had been in full work and had eaten and drunk his usual quantity without excess in either respect. At this time his attention was directed by a sensation of itching to the back of his right shoulder, and on putting his finger to the part, he found a small elevation about as big as a barley-corn and very tender to the touch. This grew rapidly and became the seat of intense pain, and continued to increase in size till his admission, but had been less painful for a few days preceding it. When he came to the Infirmary a large elevated mass existed behind the right shoulder, of circular form, about six inches in diameter, rising gradually from the level of the skin around: of livid red colour surrounded by brighter redness of an inch or two of the adjacent skin. Its circumferential part was of brawny consistence, while the central part was soft and pulpy, but not fluctuating, and in this central part there were numerous small circular apertures, which did not admit the probe for more than a very short distance; the instrument could be passed a little way under their margins, which were formed by a vascular superficial layer as thin as paper. At the centre of the tumour these openings were confluent.

On the day of the patient's admission Mr. Syme made a very free crucial incision through the tumour, extending down to its very base, and reaching a little way into the bright red surrounding skin. A good deal of bleeding occurred, and the colour of the tumour became rapidly and very remarkably changed to a pale bluish-red tint. The cut surface, which in the centre measured nearly two inches perpendicularly, presented numerous small collections of pus scattered through it, and many spots of yellow lymph; the rest of the tissue was evidently the dermis expanded by the inflammatory exudation, and towards the centre of the tumour in a shreddy sloughy state. The patient was not under chloroform, and says he hardly knows whether the pain of the incisions was worse than that which he had suffered from the carbuncle a few days before admission. Mr. Syme ordered milk diet, which has been gone on with to the present time (February 14), while linseed-meal poultices have been applied twice a day. Under this treatment the carbuncle has daily improved, induration diminishing and the mass melting down, partly in the state of slough and partly in that of pus; the surrounding redness is almost totally gone, no extension whatever of the disease having occurred since the incisions were made. The pale tint of the skin that occurred at the time of the incisions never became deepened, except at one part, where the interval between the incisions was greater than elsewhere, and there it remained red and hard for a day or two; but there also the free drain afforded by the incisions has some days ago removed both redness and induration. Two days after the incisions were made, he regained his appetite, which he had lost ever since the carbuncle became intensely painful, though not for several days after the commencement of the disease.

A few days after I again made a careful examination of the affected part. At this time the sections of the carbuncle made by the incisions were assuming a healthy appearance, particularly towards the circumference of the mass. These sections were now covered with granulations, and this, together with their great thickness, gave them an appearance certainly very unlike that of sections of the dermis. The incisions had, however, extended a little beyond the carbuncle into the healthy skin around, and on tracing the sections outwards to the parts where the skin was healthy, I found that the thick diseased parts passed insensibly into the sound portions, whose sections were also covered with granulations, and differed from the diseased only in their thickness.

The slough soon separated completely, leaving the external portion of each of the four flaps made by the crucial incision, and these gradually assuming the character of healthy skin, a granulating sore remained, whose cicatrization presented nothing remarkable.

Remarks.—This case illustrates some important points in the pathology, aetiology, and treatment of carbuncle. Mr. Syme long since pointed out [1] that carbuncle is essentially a disease of the true skin, that it is by no means necessarily connected at its outset with an impoverished or enfeebled state of body, although, doubtless, dependent on some constitutional vice, and that being an inflammation of peculiar intensity, it requires in its early stages general antiphlogistic treatment, and local blood-letting, in the form of free incisions, which, if practised sufficiently early, cut short the inflammation, and prevent it from running on to sloughing.

The case before us was a typical example of carbuncle, and its commencement as a pimple in the skin combines with the appearances which it presented on admission to show clearly that the pathology above alluded to is correct, so far as this individual case is concerned.

In a case of extensive carbuncle in the gluteal region which occurred about a month earlier, I was fortunate enough to obtain a slice from a part in an early stage of diseased action. This slice, which was cut perpendicular to the surface, included a small part of the subcutaneous fat, which was perfectly healthy. The dermis, however, was greatly thickened, and presented the appearance of numerous spots of greenish-yellow lymph intersected by bluish glistening bands of fibrous tissue, the dense structure of the corium being expanded into a loose network, in whose meshes the lymph lay. The only part of the dermis that did not contain more or less of this deposit of lymph was a very thin and highly vascular layer immediately beneath the epidermis. The microscope showed that the blood-vessels of the most superficial part of the corium, including the

[1] Vide *Principles of Surgery*, by James Syme, first edition, 1831, p. 610.

papillae, were gorged with blood. This layer was about equal in thickness to the epidermis (which is thin in this region), and corresponds to the part which formed the margin of the openings in Davidson's case, described in the above report as being as thin as paper. A superficial observer might suppose this thin layer to be the skin, and regard all parts beneath it as subcutaneous tissue; but it required only a little careful observation to perceive its true relations. I confess that I had previously been accustomed to look upon carbuncle as essentially a disease of the subcutaneous tissue, but this slice convinced me, as it did every one to whom I showed it, that in that case at least the cutis vera was the seat of the disease; and it is to be observed that this, like Davidson's, was a fine example of the affection in question. No doubt, the subcutaneous textures may, and often do become affected secondarily, but the important practical fact which these two cases appear to establish, is that the great mass of a carbuncle is composed of thickened dermis, which may be freely incised without fear, whereas the subcutaneous textures in some regions contain important parts which it is very desirable to avoid. It may be remarked that the extraordinary expansion which carbuncle produces on so dense, and, at the same time, so sensitive a structure as the dermis, sufficiently accounts for the intense pain that always accompanies it.

With regard to the cause of the disease, it must be confessed that in the case above reported, none can be assigned. According to the patient's own account, he was in strong active health at the time when the carbuncle commenced, neither plethoric nor the opposite, and no irregularity had occurred either in his diet or in his employment. The constitutional vice, of whatever nature, was latent.

The free incisions made throughout the diseased mass were productive of the most palpable benefit, and evidently cut the disease short at once; and although the central part was already in the state of slough at the time of the patient's admission, yet considering that the size of the tumour was then still increasing, I cannot doubt that the red brawny circumferential parts, which afterwards recovered their natural characters, would have sloughed if the incision had not been carried freely through them. As the disease yielded to the local treatment, the patient recovered his appetite, which he had long lost, but he never grumbled at his milk diet, although it was inadvertently continued much longer than Mr. Syme had intended.

It will probably be tedious to some to read so minute a description of an affection with which they have long been familiar; but to those who do not happen to have examined the disease carefully themselves, and who know that a different pathology is commonly taught, the importance of the subject will, I hope, make the particulars which I have given acceptable.

ON THE EARLY STAGES OF INFLAMMATION

[*Philosophical Transactions*, Vol. cxlviii, Part II for 1858, p. 645.]

Received June 18—Read June 18, 1857.

INTRODUCTION

THE morbid process designated by the term Inflammation, being one to which every organ and probably every tissue of the body is liable, and comprehending as it does in its progress and consequences by far the greater number of the ills to which flesh is heir, possesses a deeper interest for the physician or surgeon than any other material subject which could be named. The practical importance of inquiries tending to elucidate the essential nature of this process, has been for centuries recognized by all enlightened members of the medical profession; for it is obvious that just views regarding it must tend to promote the establishment of sound principles in the treatment of the diseases which it produces. At the present day more especially, when theory is allowed such free scope, and is permitted to attack the most time-honoured rules of practice, we stand in peculiar need of the beacon-light of correct pathology to enable us to steer a safe course amid the various conflicting opinions which assail us. Yet so far from our knowledge of inflammation being in a satisfactory condition, authorities are at variance upon the fundamental question, whether it is to be regarded, in accordance with John Hunter's opinion, as active in its nature, and consisting in an exaltation of the functions of the affected part, or whether it should not rather be considered a passive result of diminished functional activity.

In seeking for the solution of this great problem, we cannot expect to gain much from the contemplation of the more advanced stages and results of inflammation, such as copious exudation of lymph, suppuration, ulceration, or gangrene. When any one of these has taken place, the nature of the original disease is masked to a great extent by the subsequent changes; and the cell-development which occurs in lymph after its effusion, is no more proof of activity in the inflammatory process, than the loss of the vital powers in gangrene can be accepted as evidence in the opposite direction. It is upon the first deviations from health that the essential character of the morbid state will be most unequivocally stamped, and it is therefore to the early stages of inflammation that attention must be chiefly directed in this inquiry.

If the palm of the hand be chafed by long-continued friction, as for example in rowing a boat, the first thing that will be observed, when attention has been directed to the part by a feeling of uneasiness, will be that the skin is redder than natural, implying that the vessels are abnormally loaded with blood, and if the irritation be continued, the cuticle will be raised in the form of a blister. If, now, the loosened epidermis be artificially removed on the earliest occurrence of effusion, a scarlet raw surface will be exposed ; and on pressing the tender dermis firmly with the finger, and suddenly removing the pressure, it will be found that while the redness will for the most part have momentarily disappeared, there will be many minute red points from which the blood cannot be expelled. This shows that, while the blood is in part still free to move, there are some minute vessels completely clogged with it. Again, if a portion of mustard be placed on the skin covering the dorsal aspect of one of the fingers, abnormal redness will very speedily be produced, which in the first instance disappears completely on pressure ; but, if the mustard has been kept on long enough, can be only imperfectly dispelled ; and if the application be still longer continued, vesication will be the result. I had lately the opportunity of examining the brain of a man who had died of tetanus, complicated with incipient meningitis; the post mortem appearance of the latter being maculiform congestion of the pia mater. Having stripped off a portion of the affected membrane, and carefully washed away with a camel's-hair brush the cerebral substance adhering to it, I applied the microscope to one of the affected spots, and found that all the minute vessels were filled with crimson blood, while those of the surrounding parts were comparatively pale. It was evident that the red corpuscles were, in the former, so closely crammed together as to produce the appearance of a uniform mass, while in the latter they were present only in their usual proportion to the liquor sanguinis. Thus it appears that in the human subject, inflammation, whether induced by mechanical irritation or by an acrid application such as mustard, or of spontaneous origin, is characterized at an early period by a certain amount of obstruction to the progress of the blood through the minute vessels ; a phenomenon, which it is therefore of great importance to understand.

It fortunately happens, that we have, in the transparent web of the frog's foot, an opportunity of observing with the utmost facility the circulation of the blood in the living animal, and of watching the effects produced upon it by irritating causes. It may naturally appear very doubtful whether observations made upon creatures so low in the animal kingdom as the amphibia, can with propriety be brought to bear upon human pathology. A few facts will, however, suffice to show that no such doubts need be entertained. If a portion of moistened mustard be placed upon the web of a frog, tied out under the microscope, the blood-vessels will soon be found abnormally red ; and if the application be continued long enough, all the capillaries will become choked with corpuscles so closely packed as to present the appearance of a uniform crimson mass; and by and by the epidermis will be found raised in the form of a blister over the part on which the mustard lay. These effects are precisely similar to those which we have seen to be produced by it upon the human skin; and before effusion has taken place, the vessels of the affected part exactly resemble those of the congested spot of inflamed pia mater above described. Again, if dry heat be made to act upon a part of the frog's foot, there will result, in proportion to the elevation of the temperature and the duration of its action, undue redness of the vessels from accumulation of the blood-corpuscles; and if the burn have been sufficiently severe, vesication will soon take place as in the human subject. These and other similar cases indicate that the early stages of inflammation are alike in man and in the frog, and this conclusion is fully confirmed by examination of the bat's wing, which furnishes the means of watching the effects of irritants upon mammalian circulation. The very small size of the blood-corpuscles, and some other circumstances, render that animal much less suitable for the investigation than the frog; but with the use of high powers of the microscope and a little pains, the same sort of experiments can be made with both: and the careful observations of Messrs. Paget and Wharton Jones, and, I may add, also my own more limited experience with the bat, have shown that in all the details that can be observed, a complete similarity obtains between the effects of irritation upon the circulation in the two creatures. We may therefore rest fully satisfied that conclusions arrived at from the study of the early stages of inflammation in the foot of the frog will apply in all strictness to the same morbid process in man.

It is well known that the field of observation thus afforded has not been allowed to remain uncultivated. Since the microscope has been brought to its present state of perfection, not to speak of a previous period, men of established scientific reputation have devoted much patient labour to it; and any one who now enters upon this inquiry has the great advantage of possessing faithful records of accurate observations made by many able predecessors. But the number and discordance of the views entertained by different authorities regarding the cause of the 'stasis' of the blood in inflammation, are sufficient evidence either that the subject demands further investigation, or else that it lies beyond the reach of human means of research.

Having been called upon in the capacity of a teacher of surgery to attempt an explanation of the matter to others, I felt bound to do my best, by personal observation, to form a judgement for myself; and several new facts which I have unexpectedly met with appear to throw such fresh and clear light upon the nature of disease, that I venture to submit them to the Royal Society.

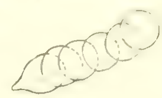
P 2

SECTION I

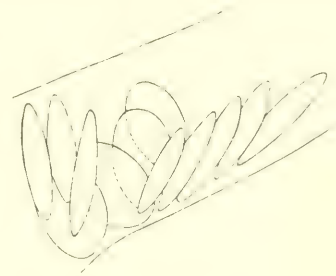
On the Aggregation of the Corpuscles of the Blood.

The tendency of the corpuscles of the blood to aggregate together, constitutes, as we shall see, an important element in the cause of the obstruction which they experience in the vessels of an inflamed part. It is therefore desirable that we should be acquainted with the nature of the phenomenon.

If a drop of human blood just shed is placed between two plates of glass and examined with the microscope, the red corpuscles are seen to become applied to one another by their flat surfaces, so as to form long cylindrical masses like piles of money, as first observed in 1827 by my father and Dr. Hodgkin ; and the terminal corpuscles of each ' rouleau ' adhering to other rouleaux, a network is produced with intervals of colourless liquor sanguinis. Rapid movement of the blood prevents this occurrence, but it commences as soon as the corpuscles approach to a state of quiescence, and I have seen short rouleaux already present in a drop drawn from my own finger within ten seconds of its emission. In this respect the aggregation of the red corpuscles differs from the coagulation of the fibrine, which does not begin till some minutes after withdrawal from the vessels. There is, in fact, no connexion whatever between the two processes, as is clear from the circumstance that if a drop of blood is stirred with a needle while coagulation is taking place, so as to remove the whole of the fibrine, the corpuscles, which have been separated from one another by the agitation to which they have been subjected, aggregate again in the serum in the same manner as they did at first in the liquor sanguinis. The beautifully regular form of the long masses of corpuscles has suggested to some persons the idea of the operation of some peculiar vital attraction in their formation, while by others the aggregation has been supposed due to merely physical causes, but has never, I think, received a complete explanation. For my own part, I am satisfied that the rouleaux are simply the result of the biconcave form of the red discs, together with a certain, though not very great degree of adhesiveness, which retains them pretty firmly attached together when in the position most favourable for its operation, namely, when the margins of their concave surfaces are applied accurately together, but allows them to slip upon one another when in any other position. There is never to be seen anything indicating the existence of an attractive force drawing the corpuscles towards each other : they merely stick together when brought into contact by accidental causes. Their adhesiveness does not affect themselves alone, but other substances also, as may be seen when blood is in motion in an extremely thin film between two plates of glass, when they may be observed sticking for a longer or shorter time to one of the surfaces of the glass, each one dragging behind it a short tail-like process ; and as the movement of the blood diminishes so as to permit the formation of rouleaux, the latter may be not unfrequently seen adhering in the same way by one of their terminal corpuscles, as represented in the accompanying diagram.



That the cylindrical character of the aggregated masses is an accidental result of the shape of the blood-discs, is evident from the fact, that in the frog, although the same tendency to agglutination of the corpuscles exists as in mammalia, yet, as their biconvex form renders it mechanically impossible for them to be applied to one another throughout their entire circumference, they become arranged in groups of an irregular form, as is shown in the annexed sketch of blood contained in a small vein of the frog's web.



Again, different specimens of mammalian blood differ very much in the amount of adhesiveness of their corpuscles ; and when this property exists beyond a certain degree, the discs stick together by any parts that happen to come first in contact, and retain that position more or less, so that the result is the formation, not of rouleaux, but of irregular confused masses. The most striking example which I have seen of this was presented by the blood of a bat, which had lived some days after having been severely wounded. In that case, chains of red discs might be seen adhering firmly by their edges, notwithstanding considerable force of traction operating upon them, and before they at last gave way tail-like processes of considerable length were drawn out between every pair of corpuscles, indicating that they were very adhesive. These facts seem sufficient proof of the correctness of the view above expressed regarding the cause of the rouleaux.

The adhesiveness of the red corpuscles does not appear to be a vital property. When the fibrine has been removed from a drop of blood during the progress of coagulation, the rouleaux will form again, after being broken up, as many times as the experiment is repeated, until the blood becomes thick from dryness ; and if evaporation be prevented by Canada balsam placed round the plate of thin glass, with suitable precaution against the approximation of the two plates, the rouleaux will remain perfect for several days (e.g. fourteen in one experiment of the kind), after which the very slow chemical action of the balsam upon the blood gradually renders it confusedly red and opaque. Gum mixed with blood seems to preserve it, like a pickle, from decomposition for a very considerable period; and if a piece of wet lint be suspended above such a specimen so as to prevent evaporation, the corpuscles will retain their adhesiveness for a long time (e.g. twenty-four days in one instance), until the water communicated to the mixture by the artificially damp atmosphere gradually renders them non-adhesive. These experiments were made in winter, when the low temperature prevents rapid decomposition; but it appears unlikely that even at that period of the year a part of the human body should retain any vital properties after having been left three and a half weeks mixed with strong gum, which, it is to be observed, alters very much the form and appearance of the corpuscles.

Both in man and in the frog the white corpuscles also are found aggregated together more or less in a drop of blood examined microscopically, and indeed they adhere much more closely than the red ones both to the glass and to one another; but as they are not disc-shaped, but globular, they do not become grouped into rouleaux, but into irregular masses, which, in consequence of their colourless and transparent character, are apt to pass unnoticed, or to be mistaken for masses of coagulated fibrine. If a portion of blood be allowed to run in between two plates of glass nearly in contact with one another, the white corpuscles will be found sticking together near the edge of the glass at which the blood entered, the blood having been as it were filtered of white corpuscles as it passed on; and this is not due to the greater size of the colourless corpuscles than the red, for I have seen it occur with frog's blood when there was room enough between the plates for the red corpuscles to lie edgewise, their transverse dimensions being greater than the diameter of a white corpuscle.

The red corpuscles also often adhere to the colourless ones.

It will be seen hereafter that the corpuscles of blood within the vessels of the living body present great varieties of adhesiveness, according to the amount of irritation to which a part may be subjected; such variations are also met with in blood outside the body, in consequence of differences in the quality of the plasma.

If a drop of very thick solution of gum-arabic, freshly prepared and free from acidity, be added to about four drops of blood, the red corpuscles of the mixture will be found to aggregate much more speedily and more closely than those of ordinary blood, a fact ascertained some years ago by Mr. Wharton Jones and some other observers.[1] The result is the formation of dense orange masses with large colourless interspaces, but without much regular appearance of rouleaux. On closely examining such a specimen, the red discs are seen to be much diminished in breadth and increased in thickness, and exhibit an

[1] *Guy's Hospital Reports*, vol. viii, p. 73.

extreme degree of adhesiveness, sticking together indifferently by their edges, or any other parts that happen to come first ; and if one of the masses be stretched so as to break, the separating corpuscles become drawn out into long viscid processes, which at length give way in the middle, and each half is drawn into its respective corpuscle.

This remarkable effect cannot be accounted for by the mere viscidity of the plasma, which would not make the corpuscles adhere to each other more intimately than usual, unless they had themselves experienced some change, of which, indeed, their altered form is conclusive evidence. Further, if a very small quantity of acetic acid be added to the gum before mixing it with the blood, the corpuscles will be found to have lost altogether their adhesive character, although the mixture may be made viscid to any degree that may be desired. A little acid perspiration on the finger appears to prevent entirely the formation of rouleaux in a drop of blood taken from it ; but after the finger has been washed, the usual appearances present themselves when more blood is drawn. Diminished adhesiveness of the red corpuscles is also the earliest evidence of the chemical action of tincture of cantharides and croton oil on the blood of the frog. A similar effect is produced when a drop of human blood is shed into a little fresh almond or olive oil on a plate of glass, and stirred slightly so as to break up the blood into minute drops. On microscopic examination of such a mixture, one sees the red discs aggregated as usual in the interior of the larger drops ; but at their exterior, which is in contact with the oil, and throughout the smaller drops, the corpuscles are somewhat altered in form, being of less diameter, but thicker, though still in the form of discs, and at the same time they are found to have lost every trace of a tendency to adhere together ; and when present in a thin layer of blood they stand apart at equal distances from one another, as if exercising a mutual repulsion, at the same time exhibiting molecular movements. If a drop of blood freshly shed upon a glass plate be stirred with a needle in an atmosphere of chloroform vapour, the rouleaux will be found to form less perfectly in proportion to the time that the chloroform has acted, until, if the period be as long as thirty seconds, the corpuscles will be all cup-shaped, and will exhibit no disposition to aggregate. But no effect is produced on the formation of the rouleaux by stirring a drop of blood in the same way for a much longer time in an atmosphere free from chloroform. The aggregation of the corpuscles is not prevented merely by their becoming cup-shaped, and therefore unable to apply themselves to each other as usual. For the vapour of caustic ammonia, while it renders the corpuscles cup-shaped, seems rather to increase than to diminish their adhesiveness and aggregating tendency, and a temperature of about 32° Fahr. has similar effects with the alkali.[1] Even in the mixture of blood and gum many of the corpuscles are cup-shaped, though adhering together with peculiar tenacity.

Whether or not it will ever be possible to explain these curious facts upon chemical principles seems very doubtful ; but in the meantime, what appears most striking about them, and what most concerns the present inquiry, is that great effects may be produced upon the adhesiveness of the red corpuscles, both in the way of increase and diminution, by very slight changes in the chemical qualities of the plasma.

The galvanic current produces no effect upon the aggregation of the red corpuscles, either of man or of the frog, as I have ascertained by placing the fine platinum-wire extremities of the poles of a powerful battery a short distance from one another between two slips of glass beneath the microscope, then completing the circuit by shedding a drop of blood between the plates, and immediately observing the result. In several such experiments I invariably found that aggregation took place as usual, and the only effect produced by the galvanism was a chemical change in the blood, dependent on electrolysis, gradually developing itself in the immediate vicinity of the poles, and causing solution of the corpuscles.

The buffy coat in inflammatory blood was first explained by Mr. Wharton Jones,[2] who showed that it resulted from the red corpuscles aggregating more closely than usual, and therefore falling more rapidly through the lighter plasma, so as to leave the upper portions completely before the occurrence of coagulation. It was supposed by the same authority that this peculiarity of the red discs

[1] Since this paper was read, I was told by a gentleman well known in the scientific world, that he had observed, many years ago, that if blood was shed upon a plate of glass previously heated to the temperature of 100° Fahr., the red corpuscles showed no disposition to aggregation till the glass cooled, when the blood became killed, as he supposed, by the unnaturally low temperature. This appeared to me entirely irreconcilable with the fact that in the frog the red corpuscles aggregate immediately after the blood has been shed, although there is no material difference between the temperature of the air and that of the body of the animal. But, if true, it would have important bearings, to which I need not here allude, upon the essential nature of inflammation. I have therefore thought it well to make some experiments upon the point. The plate of glass upon which the blood was to be placed was warmed by immersion in water of a known temperature, and quickly but carefully dried. A drop of blood from my own finger was then at once shed upon it, and without loss of time covered with a piece of thin glass, which had been kept warm by being laid upon a metallic plate of the same temperature as the water. By proceeding in this way, I was able to make observations upon the blood very soon after it had been shed ; and when the glass was about 100° Fahr., the aggregating tendency was found just the same as in ordinary cases, and I detected short rouleaux already formed within five or six seconds of the escape of the blood from the vessels of the finger. The same state of things continued when the water was as high as 136° ; but when its temperature was carried up to 155°, the red corpuscles lost their disc shape and some of them appeared to become broken up, and no rouleaux were formed either while the blood remained warm or after it had cooled. From these results, it is evident that heat does not interfere at all with the aggregating tendency of the corpuscles, unless it is sufficiently great to act upon them chemically.

[2] *British and Foreign Medical Review*, October 1842.

was due to increased fibrine in solution, rendering the liquor sanguinis abnormally viscid, and so operating like the admixture of gum above alluded to. But the fact that the corpuscles aggregate as closely after the fibrine has been removed as before, appears quite opposed to such a view. I have examined many drops of my own blood, before and after the removal of its fibrine, with the special object of ascertaining this point, and have never been able to detect any material difference between the aggregation in the two sets of cases. In the blood of the bat before mentioned, which was probably suffering constitutionally from inflammation, the corpuscles continued to retain their excessive adhesiveness for a whole hour after coagulation of the fibrine. I once made a similar observation on a specimen of horse's blood,[1] which, as is well known, presents the buffy coat in the state of health. Having divided the clot vertically several hours after coagulation had occurred, my attention was attracted, on looking at the section, by minute red points, like grains of sand, lying in the lower part of the buff, just above the coloured portion of the coagulum. On microscopic examination of a small piece containing some of them, they proved, as I expected, to be masses of aggregated red corpuscles, but with the peculiarity of being compact and globular instead of presenting the usual appearance of a network of rouleaux, and it was evident that the corpuscles had been excessively adhesive at the time when aggregation took place. Some of the red discs were now squeezed out from the fibrinous mass in which they lay, and as they escaped into the surrounding serum they at once adhered firmly in that fluid, forming again compact globular masses, such as, if in freshly drawn blood, would necessarily give rise to the buffy coat ; so that their adhesiveness seemed to have been in no way affected by the withdrawal of the fibrine from solution. It may of course be urged, that the fibrine, when in solution, may have impressed upon the corpuscles an adhesiveness which they retained after soaking for hours in serum, but this seems a very unlikely hypothesis. I suspect, therefore, that the peculiarities of the corpuscles of inflammatory blood are the result of other changes than the excess of fibrine.

From the facts detailed in this section, it appears that the aggregation of the corpuscles of blood removed from the body depends on their possessing a certain degree of mutual adhesiveness, which is much greater in the colourless globules than in the red discs ; and that, in the latter, this property, though apparently not depending upon vitality, is capable of remarkable variations in consequence of very slight chemical changes in the liquor sanguinis.

[1] This observation was made subsequently to the reading of the paper, viz. in November 1857.

SECTION II

On the Structure and Functions of the Blood-vessels

An acquaintance with the anatomy and physiology of the vascular system is indispensable to a successful study of the deviations from health exhibited in the circulation of the blood through the vessels of an inflamed part ; it is not, however, intended to give here a full account of the subject, but merely to dwell upon some important points on which differences of opinion prevail.

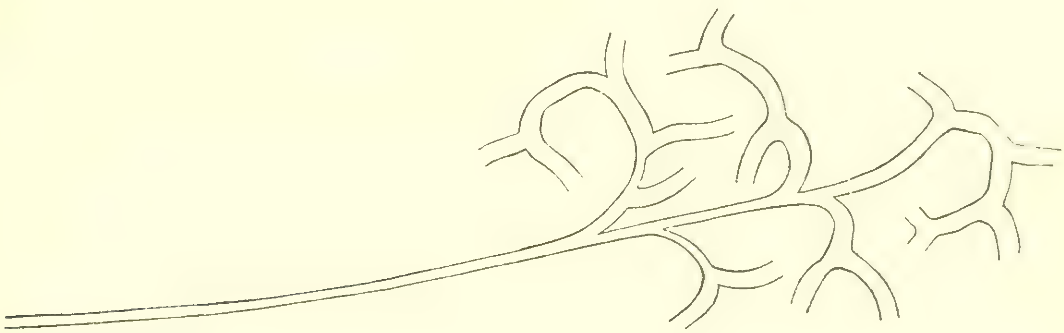
It has long been a debated question whether or not the capillaries possess contractility, and there is still some difference of opinion among authorities upon the subject. With a view to throwing light upon this important point, I investigated carefully the structure of the minute vessels of the frog's foot ; dissecting them out from between the layers of skin composing the web, so as to render their constituent material capable of clear definition with the microscope. The chief results have been communicated to the Royal Society of Edinburgh, in a paper that will shortly appear in their *Transactions*, 'On the Structure of Involuntary Muscular Fibre.' [1] I need therefore merely repeat here, that while the capillaries were proved to consist, as has been long known, merely of a delicate homogeneous membrane beset with occasional nuclei, the minute arteries, some of them even less in calibre than average capillaries, were found to possess three distinct coats, namely, an external layer of cellular tissue, in variable quantity, longitudinally arranged, an internal extremely delicate lining membrane, and an intermediate circular coat, which constituted the principal bulk of the vascular parietes, and which, when highly magnified, was found to consist of a single layer of muscular fibre-cells, each wound spirally round the internal membrane so as to encircle it from one and a half to two and a half times.

Now when we consider the properties of muscular fibre-cells, which, as is shown in the paper referred to, are capable of contracting in the pig's intestine as much as to one-tenth of their length, it is impossible to conceive a more efficient mechanism for the constriction of a tube than is provided in these minute arteries. On the other hand, the capillaries are totally destitute of any structure known to be contractile. The changes of calibre which occur in the vessels of the living web are in perfect harmony with this anatomical description ; for while the arteries, even to their smallest branches, are sometimes constricted to absolute closure, and at other times widely dilated, the capillaries are never found to be entirely closed, nor to present any variations in diameter, which are not explicable by elasticity of their parietes.[2]

[1] Printed at p. 15 of this volume.

[2] In this respect I merely confirm the observations long since made by Messrs. Paget and Wharton Jones.

The sketch given below represents the calibre of an artery dividing into minute branches, with the capillaries into which they poured their blood. At the time when it was drawn, the artery and its branches were in a state of spontaneous contraction, yet the capillaries retained their full average dimensions. After a while the artery became so much more contracted as only to admit single corpuscles even through the main trunk ; yet still the capillaries fed by it did not appear affected in calibre. This is but one example of what I have observed times without number.



The capillaries, though not contractile, are highly elastic, and by virtue of this property are capable of considerable variation in capacity, according to the distending force of the current of blood. Figs. 3 and 4 of Plate III (see p. 68), traced with the camera lucida, show, besides the pigment in two chromatophorous cells of the frog's foot, part of a capillary in nearly extreme conditions in point of calibre. In Fig. 3 the vessel is about equal in diameter to the length of a red corpuscle, while in Fig. 4 it is so narrow that the corpuscles in it are pinched transversely and elongated. When the capillaries are most distended, their parietes are much thinner than when shrunk to their smallest dimensions ; an estimate may be formed of the difference by comparing the close proximity of the corpuscles to the outer bounding line of the vessel in Fig. 3 with the considerable interval in Fig. 4, that interval representing the apparent thickness of the wall of the vessel. It is to be observed that the frog had been killed in a manner involving considerable haemorrhage before Fig. 4 was traced, so that the capillaries were then little, if at all, distended with blood. The thinness of the walls of the capillaries, as compared with the small arteries, is, doubtless, calculated to favour the mutual interchanges which must take place between the blood in them and the tissues in their vicinity.

It is believed by some eminent authorities that mutual attractions and repulsions subsisting between the nutrient fluid and the tissues among which it flows, become a source of movement in the blood and assist its flow through the capillaries; while others regard the heart as the sole cause of the circulation: and the difference of opinion on this fundamental point in physiology involves discordance in pathological theory, for some who hold the former view consider the changes which occur in the circulation at the commencement of inflammation, to be principally owing to modifications of the 'vital' moving force.[1] The view that such a cause of movement exists, has been supported partly by argument drawn from the phenomena of inflammation: but these, as we shall see, require a very different interpretation. It has also been based upon a supposed analogy between the circulation of the blood in the higher animals and certain movements observed to occur without any visible source of mechanical power in tubes and cells in the vegetable kingdom, and, as was thought, also in some of the lower forms of animal life: but though a resemblance may probably exist between some of these and the movements occurring in the processes of secretion and absorption and the circulation of nutrient fluid among the tissues of intercapillary spaces and non-vascular parts, the progress of modern discovery tends to show that the comparison is altogether inapplicable to the sanguiniferous system. It would, I think, be out of place to enter fully into this discussion on the present occasion, but my own experience with the frog leaves no doubt in my mind that in that animal contractions of the heart are the only cause of the circulation. I will content myself with mentioning two observations bearing upon this question. The first of these has reference to certain movements which occur for a considerable time after cessation of the heart's action, and which, though of trivial and uncertain character, have had much stress laid upon them in this discussion. I have ascertained by observations made in several different cases, that they are produced by occasional spontaneous contractions and relaxations of the arteries. These changes in the calibre of the vessels continue, even in an amputated limb, for days after severance from the body:[2] I have repeatedly watched them taking place, and seen them give rise to the movement of the blood.

The other fact to which I will allude appears to me to decide of itself the question at issue. Having occasion to examine, under chloroform, some very small frogs, measuring about an inch from the tip of the nose to the end of the coccyx, I found that the blood in the capillaries invariably flowed in a stream pulsating synchronously with the beats of the heart, which were visible through the parietes of the thorax: and however mildly the anaesthetic was adminis-

[1] See *Outlines of Pathology and Practice of Medicine*, by W. P. Alison, M.D., F.R.S.E., &c., 1884, pp. 115 et seq.

[2] See the preceding paper on the parts of the Nervous System which regulate the Contractions of the Arteries, p. 27 of this volume.

tered, the motion was commonly exceedingly slight between the pulses. Not unfrequently, although the arteries remained of full size, the blood moved in jerks, with considerable intervals of absolute stillness between the successive impulses which the contractions of the heart occasioned; yet no accumulation of corpuscles was produced in the capillaries, however long the animal was kept under observation. Had any other cause of motion than the action of the heart operated upon the blood, there must have been a continuous flow, however much accelerated at each pulse; for I must add, that there was nothing whatever of recoil after each onward movement, nor anything indicating obstruction to the progress of the blood.

Thus in these cases of intermitting capillary flow, it was matter of direct observation that the heart was the sole cause of the blood's motion; and as we know that in an animal under the influence of chloroform the changes of the blood from arterial to venous, and vice versa, continue to occur in the systemic and pulmonary capillaries, and as we have every reason to believe that the processes of nutrition in the different parts of the body go on then as usual, these cases appear to prove absolutely that the forces which are concerned in the mutual interchanges between the tissues and the nutrient fluid do not cause any movement whatever.

But even supposing that it were admitted, for the sake of argument, that the vital affinities do, under ordinary circumstances, cause some movement of the blood, but lose that power in an animal under chloroform, such an admission would hardly affect the discussion regarding the cause of stagnation in inflammation; for in a frog fully under the influence of the anaesthetic, in which, as we have seen, the heart is the only cause of circulation, all the phenomena that result from irritation of the web take place precisely in the same manner as in one to which the narcotic has not been administered. The fact that the heart, even though much enfeebled by chloroform, is capable, unaided by any other force, of maintaining the circulation for an indefinite period without the occurrence of obstruction in the capillaries, or any undue accumulation of corpuscles in them, affords positive proof that any other cause of movement which may be conceived to exist when chloroform has not been given, must be altogether insignificant, and that the cessation of its operation does not give rise to stagnation of the blood.[1]

[1] Dr. Sharpey has for many years alluded in his lectures to the circumstance that, the weaker the animal, the more do the effects of the successive cardiac impulses show themselves in the capillaries of the webs, as evidence that the action of the heart is sufficient to account for the circulation. He also informs me that he has frequently verified the observation of Spallanzani, that in the gills of the tadpole the flow of the blood ceases completely in the intervals between the pulses produced by the ventricular contractions.

The veins of the frog's web afford very little evidence of contractility; but a small amount of unstriped muscular tissue, transversely arranged, is distinctly to be seen in the larger venous branches; and on one occasion I observed a very considerable degree of local contraction, as measured from the outer borders of the external coat of a vein running through a small area which I had pinched forcibly with forceps. I have also seen one expand on sudden dilatation of the arteries of the web, so that its diameter increased from twelve to fourteen degrees of a micrometer; but this is perhaps explicable by elasticity.[1]

It has been already mentioned that the arteries undergo spontaneous variations of calibre. Such changes are constantly going on at varying intervals, there being nothing of a rhythmical character about them. A struggle on the part of the animal is generally accompanied by a very considerable constriction of the arteries, and sometimes by absolute closure of them. The contraction usually begins a very short time before the motions of the body, so that the struggle can commonly be predicted by the appearance of the vessels; and dilatation occurs when the creature becomes quiet. Hence the changes of calibre are evidently under the control of the nerves. An account of an inquiry into the parts of the nervous system by which this control is exercised, will be found at p. 27 of this volume; and from the experiments there recorded, it will be seen that either extreme constriction or full dilatation of the arteries of the web may be induced at pleasure, by operating upon the spinal cord. A very good opportunity is thus afforded for studying the effects produced upon the capillary circulation by changes of calibre in the arteries, without employing any means acting directly upon the foot. This is a matter of very great importance, for applications made to the web for the purpose of inducing alterations in the dimensions of the vessels, give rise at the same time to other consequences of irritation, which complicate such experiments in a most deceptive manner, so as to have misled, as I believe, some of the best observers who have devoted attention to this subject.

The following account embodies the results of numerous observations in

[1] Since the reading of this paper I have noticed striking examples of the contractility of the larger veins in the higher animals. Thus, on exposing the jugular in a living calf, I have seen a particular part of the vessel irritated by the process of dissection shrunk to about a third of its previous calibre. In the human subject, too, when amputating lately at the shoulder-joint on account of contusion inflicted by machinery upon a previously healthy limb, I noticed the axillary vein reduced to about half its natural calibre at the part where it was divided, which was in the immediate vicinity of the injury. I have also had occasion to observe the post mortem contractions of the subcutaneous veins of the sheep's foot, which are carried to such an extent as to reduce the vessels from the size of a crowquil to about that of a darning-needle. The minute veins also sometimes exhibit great contractility in the higher animals, as in the irregular constrictions often seen in those of the mesentery of the mouse, and in the remarkable rhythmical variations in calibre discovered by Mr. Wharton Jones in those of the bat's wing (*Philosophical Transactions*, 1852).

which this source of fallacy was carefully avoided, the variations in the calibre of the vessels being generally either induced by operations on the cord, or else such as occurred spontaneously.

In a perfectly healthy state of the web with the heart beating powerfully, when the arteries are of about medium width, the current of blood in them is so rapid that the individual corpuscles cannot be discerned ; but in the capillaries, whose aggregate calibre is very much greater than that of the arterial trunk which feeds them, the flow is so much slower that they can be pretty clearly distinguished. When the arteries are fully dilated, if the heart continues to act with the same energy, the blood appears to move as rapidly in them as before, though of course in much larger quantity ; while in the capillaries the flow is extremely accelerated, so that it becomes as impossible to see the blood-corpuscles in them as in the arteries. On the other hand, when the arteries are considerably constricted, the blood moves more slowly through the capillaries than when the tubes of supply are of medium size, and at the same time the narrowed arteries appear to filter the blood more or less of corpuscles, which are found in smaller numbers in proportion to the liquor sanguinis in the capillaries : and if the constriction of the arteries is sufficiently great, the web is rendered quite pale in consequence of the small number of corpuscles in it, which nevertheless continue to move among the tortuous capillaries, producing in the field of the microscope an appearance something like that of a few flies playing about in a room. Finally, if the arteries are completely constricted, all appearance of flow in the capillaries vanishes, and the web has a wholly exsanguine aspect. Under these circumstances, even the veins, though still of large calibre, may contain little besides colourless liquor sanguinis, which has continued to ooze through the contracted arteries when the corpuscles have been completely arrested ; and so inconspicuous do the veins become in consequence of this change in the quality of their contents, that it may be extremely difficult to distinguish them from other tissues ; the appearance of the web on superficial observation being as if it possessed no blood-vessels at all. This remarkable condition, which, so far as I know, has not been before described, may last for several minutes in consequence of irritation of the cord, and in one case I observed it occur spontaneously, and continue for five minutes together. It appears to be comparable to the dead whiteness of the human fingers when benumbed with cold, or the perfect pallor of the cheek in faintness ; while blushing is no doubt caused by full dilatation of the arteries.

Such, according to my experience, are the effects produced upon the circulation by changes of calibre in the vessels of a perfectly healthy web. The arteries regulate by their contractility the amount of blood transmitted in a given time through the capillaries, but neither full dilatation, extreme constriction, nor any intermediate state of the former is capable *per se* of producing accumulation of corpuscles in the latter.

SECTION III

On the Effects of Irritants upon the Circulation.

It is well known that the application of an irritant substance to the web of the frog's foot is followed by changes of calibre in the blood-vessels, and also by an abnormal accumulation within them of the corpuscular elements of the blood. The first experiments which I performed upon the frog were directed to the solution of the much-debated question, whether or no the latter were a mere consequence of the former ; and although it has, I think, been sufficiently shown at the conclusion of the last section that such cannot be the case, yet it will be well to allude shortly to these experiments on account of their further bearing upon the subject of this inquiry.

It occurred to me that if, instead of the powerful irritants commonly used in these investigations, some exceedingly mild stimulant were employed, the changes in the calibre of the vessels might perhaps be produced without concomitant alterations of the blood. The material which appeared most suitable for this purpose was warm water, which is known to cause, in the human subject, increased redness without inflammation of the part to which it is applied.

Accordingly, in September 1855, I endeavoured to ascertain its effects upon the frog. In most of the experiments, the foot of the animal being stretched under the microscope upon a glass plate somewhat inclined, so that any fluid upon it might run off quickly, an assistant threw a stream of water of known temperature upon it by means of a syringe, the eye of the observer being kept over the microscope, which was provided with a micrometer in its eyepiece. In this way the effects produced by the water could be seen almost immediately after it had ceased to play upon the web, and the changes of calibre in any artery selected for observation were noted with precision. It was found that the result of the warm application was constriction of the arteries to absolute closure, generally lasting for several seconds,[1] and then giving place to dilatation beyond their original dimensions, to which they afterwards gradually returned.

[1] The period of constriction varied much in different instances, and it sometimes passed off (if it occurred at all) before it could be observed. It was best marked in a case, in which, the animal being very quiet, chloroform was not employed. The anaesthetic appears to impair the functions of the spinal cord as a regulator of the calibre of the vessels ; and its administration is generally followed by their dilatation.

The dilatation differed in different instances, being generally more decided and more permanent when the water was hotter and longer applied.[1] In one case, water at 100° thrown upon the web for a brief period caused constriction for a few seconds in the artery under observation, followed by dilatation. While the vessels were still above their usual calibre, more water of the same temperature was applied as before, and again induced contraction followed by abnormal dilatation, which was again made to give place to constriction by a third similar application : the experiments were repeated within a few seconds of each other.

When water not higher in temperature than from 110° to 140° was thrown for not longer than a second or two upon a perfectly healthy web, the changes above described in the diameter of the arteries produced effects upon the flow of blood through the capillaries, precisely similar to those mentioned at the conclusion of the last section. Thus in one such case the constriction of an artery lasted for several seconds, and was in the first instance so tight as to prevent any flow in the field of capillaries supplied by it ; then relaxing slightly, it allowed single corpuscles to pass along it with great difficulty, so that the blood became almost entirely filtered of its particles, and at the same time the force of the heart being to a great extent taken off from the elastic capillaries, liquor sanguinis almost destitute of corpuscles flowed in slow pulsating streams along the veins : finally, the dilatation becoming complete, blood of ordinary appearance rushed through with great rapidity.

If, however, such experiments had been several times repeated upon the same foot, and more especially if the warm water had acted for longer periods, another class of symptoms began to show themselves ; the corpuscles passing on less freely than the liquor sanguinis through the capillaries, and lagging behind so as to accumulate in abnormal proportion to the plasma, and stagnating completely when the force of the heart was partially taken off through contraction of the arteries, though passing on again when the vessels dilated.[2]

Thus in one case an artery under observation measuring 2° (degrees of the

[1] Water of the temperature of the room applied in the same way after warm water had been several times employed, caused complete constriction of the arteries, lasting for several seconds ; but the subsequent dilatation was very little if at all beyond the normal calibre.

[2] This effect of arterial contraction in producing accumulation and stagnation of corpuscles in the capillaries has been described by Mr. Wharton Jones as occurring in a state of health (see *Guy's Hospital Reports*, loc. cit.). The reason of this I believe to have been, that much greater care than is generally supposed is required in order to avoid any irritation whatever of the delicate webs. The vicinity of the warm hand is particularly apt to produce this effect ; and I have known it, when continued for a quarter of an hour, cause complete stagnation of the blood throughout the webs, while a very much shorter period is sufficient to induce a decidedly abnormal condition. I have myself only become fully aware of the great susceptibility of the foot of the frog to injury from warmth since the reading of this paper. An unhealthy state of the webs is indicated to the naked eye by conspicuousness of the blood-vessels. In perfect health they are quite invisible without the microscope, and in all cases the appearance of any vessel as a distinct red streak is pretty sure indication of a certain amount of irritation.

micrometer), the blood was flowing in all the capillaries supplied by it, though containing a very abnormal amount of corpuscles. After a few minutes, the vessel contracted spontaneously to $1\frac{1}{4}$°, and though this was only about a medium width, the flow of the blood became much retarded in the capillaries, and in one of them ceased almost entirely. Water of 115° Fahr. being then thrown upon the web, the calibre of the artery was raised to above 2°, and the flow was resumed in all the capillaries. A few minutes later the vessel again contracted spontaneously to $1\frac{1}{2}$°, when stagnation of the blood became nearly complete in a few of the capillaries. Water at 120° was then applied and caused constriction to a further degree, followed by dilatation to above 2°: during the constriction, the blood scarcely moved at all in the capillaries, but on the occurrence of the dilatation it again flowed in all of them.

If the applications were still further continued, the red discs became more and more closely packed, till at last they were crammed together so as to produce a uniform crimson mass, unaffected by the heart even in the widest state of the arteries.

It was perfectly clear that in these experiments the stagnation of the blood depended on something more than mere contraction of the arteries; and it also appeared impossible to account for it satisfactorily as a result of their dilatation. That inflammatory stasis might occur independently of alteration in the calibre of the vessels, was also shown by an experiment with capsicum made at this period. A morsel of this substance having been placed upon the middle of a web in which the circulation was going on in perfect health and with unusual rapidity, the effect was great accumulation of corpuscles in two or three capillaries for a very short distance round the spot where the capsicum lay, unaccompanied by any change in the vascular dimensions.

Chloroform proved to be an agent which very readily induced stagnation when locally applied; and when it was administered in the usual way by inhalation for the purpose of performing experiments with warm water, it was found necessary to protect the webs carefully from its vapour, which otherwise produced the same appearances of congestion as the hot application. In one instance in which a small quantity of the liquid had been applied to the web, I saw the red corpuscles adhering to one another by their flat surfaces, in a manner not seen in the healthy condition, and exactly as described by Mr. Wharton Jones to take place after the application of a strong solution of salt; but from the very slight tendency of chloroform to mix with water, it was impossible to believe that it had operated by way of exosmose, as was supposed by the authority just named to be the case with the saline solution.[1]

[1] It was believed that the solution of salt abstracted water from the blood as it flowed through

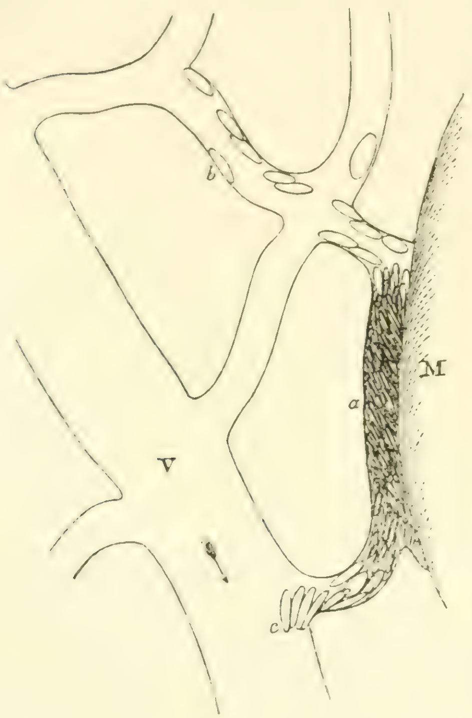
From the facts above mentioned, I became convinced that no satisfactory explanation had as yet been given of the obstruction experienced by the blood-corpuscles in the vessels of an inflamed part, and in September 1856, I again continued the investigation. Mustard being admitted to produce inflammation in any part of the human body to which it is applied, and also not appearing likely to act by way of exosmose, I selected it as a suitable irritant, and in order to study its effects accurately, placed a small portion of its moistened flour, about a line in diameter, upon the middle of the web of a large frog under chloroform. After a while, thinking that I saw stagnation in a capillary just at the margin of the mustard, I removed the latter with a camel's-hair brush, and was surprised to find that throughout the whole area on which it had lain, the capillaries were crammed with either stagnant or very slowly moving red corpuscles. The limits of the part so affected corresponded exactly with the extent of the application of the mustard, although the capillaries of adjoining parts were fed and drained by the same arteries and veins.

On the 3rd of October I made another similar experiment, selecting a part of the web where a considerable artery divided into small branches. Before applying the irritant, I had ascertained that the artery running through the area measured $6\frac{1}{2}°$ of an eyepiece-micrometer,[1] while a large vein near it had a diameter of 12°. About half a minute after the application of the mustard, when I first looked through the microscope, the arteries of the web generally were much dilated, and the flow, which had before been somewhat languid, was rapid in all its

the capillaries, and that the liquor sanguinis being consequently inspissated, the red corpuscles assumed an abnormal tendency to aggregate together (see *Guy's Hospital Reports*, loc. cit., p. 40). This view has been more recently advocated by a German writer, Fr. Schuler of Glarus (*Würzburg Verhandlungen*, 1854), with a very elaborate series of difficult experiments. One of these, however, seems almost conclusive against his theory. Having injected a solution of prussiate of potash into the veins of a frog, he applied sulphate of iron to the webs, but found that very little blue colour was produced *until the epidermis of the web was scraped away*, when it showed itself distinctly. Considering how delicate a test prussian blue is of the presence of a mixture of the two salts, this result seems to show that there is far from being the same tendency to mutual interchange between the blood in the capillaries and fluids in contact with the surface of the web, as there would be if the intervening material were dead animal membrane of the same tenuity. Were the disposition to exosmosis and endosmosis such as is assumed in the above explanation of stasis from a solution of salt, it would be impossible for the animal to live long either in water or on dry earth. In the former case the blood would soon become diluted from imbibition, and in the latter inspissated from evaporation. But it is well known that frogs will live for months in water without food, and I have kept them for weeks together upon dry earth at a temperature of about 60° Fahr., and on removing from the webs a layer of dust and exfoliated epidermis, found the circulation perfectly healthy. Since the reading of this paper, I have seen a remarkable example of the power of the tissues of the webs to resist imbibition of water in an amputated limb with the blood retained in the vessels by a ligature. Though it was kept in wet lint, the blood in the vessels showed no indication of admixture of water till the tenth day, and then only in those parts of the web in which the arteries and pigment-cells gave evidence that they had lost their vitality. For further particulars regarding this experiment see pp. 39 and 63 of this volume.

[1] The micrometer used on this occasion was differently graduated from that employed in the warm-water experiments.

capillaries. The opacity of the mustard prevented the vessels beneath it from being observed, but at a short distance from its edge the artery measured 10^c and the vein 14^c. In a few minutes the capillaries seen beneath the extreme margin of the mustard, which was slightly transparent, were observed to be of crimson colour, in consequence of their containing closely crammed corpuscles, some of which were still moving, while others were motionless. On the application of a higher power, the continuations of these capillaries immediately exterior to the mustard showed, many of them, red corpuscles sticking to their walls, and more or less obstructing the progress of the blood through them.



In the accompanying sketch of the vessels at one part, together with those corpuscles which were motionless in them, M represents the edge of the mustard, *a* a capillary partly overlaid by the mustard and crammed with stagnant corpuscles, *b* a capillary with red discs adhering to its internal surface, but still transmitting blood, while further from the mustard all the corpuscles were in motion, and consequently none appear in the drawing ; *c* was a rouleau of red corpuscles projecting from a stagnant mass into the vein V, through which the blood was flowing rapidly ; yet the rouleau, though its free end was moved to and fro by the current, was prevented by the mutual adhesiveness of its corpuscles from being broken up or detached. Thus it was evident that in the capillaries of the space covered by the mustard, the red corpuscles had an abnormal tendency to adhere both to the walls of the vessels and to one another, and were on this account accumulating and sticking within them, while almost immediately outside the mustard, the blood in the capillaries presented the same appearance as in other parts of the web. This effect was independent of changes in the calibre of the vessels, for any results of alteration in the size of the artery under the mustard must have been shared by the surrounding capillaries, which also derived their blood chiefly from it ; and that the vesse was dilated to the same degree there as elsewhere, was shown by the fact, that its branches continued throughout the experiment to transmit full streams of blood after emerging from beneath the opaque mass. I also measured some capillaries by micrometer before the application of the mustard, and again after it had caused stagnation in them, and found that their dimensions remained the same.[1]

The precise limitation of the effect produced upon the blood in these two experiments to the area covered by the mustard, showed that it was the result of a direct action of the irritant either upon the blood that flowed beneath it, or upon the tissues of the part of the web on which it lay, the blood being in the latter case affected secondarily. I made several experiments to determine whether the adhesiveness of the corpuscles in blood out of the body was increased by contact with or vicinity to mustard, placing minute portions of it between plates of glass, and shedding a drop of blood from a frog, so that it might run in between the plates, and watching the result. I could, however, detect no evidence of such change in the corpuscles as I was seeking ; whence I inferred that the blood had been only affected secondarily to the tissues in the two mustard experiments.

A careful study of the effects produced by the local application of chloroform to the web, confirmed in every respect the conclusions previously arrived at. If, while the eye of the observer is over the microscope, a minute drop of this liquid is placed with a camel's-hair brush upon the part in the field of view, it evaporates in perhaps two or three seconds ; and if the web be dry, the time of its disappearance can be distinctly seen. Yet though it has so short a time to act, it produces so powerful an effect upon the part, that the red corpuscles immediately experience obstruction to their progress, and move too slowly in abnormal numbers through the capillaries, which perhaps become entirely clogged with them ; the arteries meanwhile being in the state best adapted for easy transmission of the blood, i.e. full dilatation. In one such experiment I saw a few corpuscles sticking together in a capillary and moving with difficulty, from evident tendency to adhere to its parietes, their number gradually becoming augmented by the adhesion of others that followed, till the mass grew so large as to fill the vessel for some distance, when it finally stopped. In another case, the circulation being perfectly natural in the web,

[1] The increased pressure upon the blood in the capillaries, resulting from obstruction to the progress of the corpuscles, leads to the distension of their elastic parietes up to a certain point, but, generally speaking, not further. In the present case, before the application of the mustard, the web, irritated probably by the vapour of the chloroform, was affected with a slight congestive tendency, far short of that which induces stagnation, but yet sufficient to give rise to full distension of the capillaries. When the web has been perfectly healthy to begin with, I have seen a marked increase of calibre in the capillaries on the occurrence of stagnation in them. This I noticed particularly in a case in which caustic ammonia was the irritant employed. I would remark, however, that the eye is apt to be much deceived on this point unless the micrometer is used. Those vessels which are crammed with corpuscles, being of dark crimson colour, look at first sight larger than others, really of the same size, which contain the normal proportion of liquor sanguinis, and are therefore of pale tint.

and the corpuscles moving on at slight intervals with no tendency to adhere, on a drop of chloroform being applied, I saw the very same corpuscles instantly become checked in their progress by sticking to each other and to the capillary walls, and move on slowly in masses with considerable intervals. Thus the nature of the effect produced upon the red corpuscles of the blood when chloroform is applied to the web is the same as that caused by mustard, viz. an abnormal degree of adhesiveness; whereas the earliest evidence of the direct action of chloroform on blood out of the body is the loss of the adhesive property of the red discs, as has been mentioned in Section I.[1] That the effect on the blood within the vessels of a part inflamed by chloroform is secondary to a change in the tissues is further proved by the circumstance, that abnormal accumulation of slowly moving corpuscles may last for hours together without stagnation, as a consequence of the application of this irritant for an extremely brief period.[2] Long after all the blood which could possibly have been directly acted on by the chloroform has left the vessels, successive fresh portions continue to experience precisely similar changes in passing through the irritated area.

Heat produces similar effects. If the foot of a frog which is under the influence of chloroform be covered entirely with wet lint, except a small area of one of the webs, and a red-hot cautery iron be held for a few seconds about half an inch above the exposed part, inflammation will be excited in the area in proportion to the time of the action of the dry heat upon it; but on removal of the lint, the circulation will be found perfectly healthy in the surrounding parts. In the severer cases stagnation is universal in the exposed area, and the epidermis becomes eventually raised by the exudation of serum beneath it; but in milder instances nothing more than accumulation of slowly moving corpuscles is produced, and I have observed this state of the part to continue for hours after the heat was applied. Here again the effect on the blood was obviously not due to the direct action of the heat upon it, but to some changes which it had effected in the tissues of the part on which it had acted.

Evidence of the same kind, but still more conclusive, is derived from the effects of mechanical irritation, where the agency is free from all objection of possible chemical action on the blood. The method adopted was that of compressing a small part of the middle of the web between little pads of soft material attached to the ends of the blades of a pair of surgical dressing forceps, by which

[1] See p. 215.

[2] The gradual supervention of the effects of irritation upon the blood may be watched very conveniently by arranging a piece of lint soaked in chloroform, so that the vapour may play upon the web while the eye of the observer is over the microscope. If the chloroform be removed when the tendency to accumulation of corpuscles exists in a very slight degree, restoration to health will occur within a few minutes.

the degree of pressure could be regulated at will. The results of this treatment were identical with those of heat, as just described. If the pressure was not made too severe, no mechanical obstruction was produced in the vessels, which nevertheless became loaded with slowly moving or stagnant corpuscles; and on one occasion I observed the capillaries of an area which had been pinched, still transmitting languid streams of blood containing great excess of corpuscles several days after the injury had been inflicted, while in the surrounding parts the circulation continued perfectly healthy. Mechanical violence, like heat, chloroform, and mustard, had effected an alteration in the tissues on which it operated, in consequence of which the blood in their vicinity assumed abnormal characters; and many other facts of similar nature might be added, if necessary, to show that this is the course always followed when accumulation of corpuscles in the vessels is induced by the action of irritants.

In discussions regarding the causes of the phenomena of inflammation seen in the frog's web, the great difficulty has hitherto been to account for the puzzling fact, that while the arteries still retain that state of enlarged calibre which is best adapted for easy transmission of the blood, its accelerated movement comes to give place to unnatural retardation and ultimate stagnation. Accordingly, various theories, mechanical, chemical, and vital, have been proposed[1] to explain the transition from 'determination of blood', as the condition of dilatation of the arteries with increased flow through the capillaries has been termed, to inflammatory congestion, as the accumulation of corpuscles in the vessels may perhaps be most fitly designated. But the second simple experiment with mustard, to which I would again direct the attention of the reader, proves in a very beautiful manner that these two results of irritation are totally distinct in nature and independent in cause. The dilatation of the arteries, it will be remembered, affected not only the part on which the mustard lay, but also all the rest of the web, showing that it was developed indirectly through the medium of the nervous system; whereas the accumulation of the blood-corpuscles in the vessels below the mustard was, as we have seen, the result of the direct action of the irritant upon the tissues. The arterial dilatation in the web generally led to no changes in the quality of the blood, which, though the experiment was continued for some hours, retained to the last its natural characters, just as would have been the case had the enlargement of the vessels depended on an operation performed upon the spinal cord. The accumulation of cor-

[1] See *Pathology and Practice of Medicine*, by W. P. Alison, M.D., F.R.S.E.; *Principles of Medicine*, by C. J. B. Williams, M.D., F.R.S.; *Lectures on Surgical Pathology*, by James Paget, F.R.S.; 'Observations on the State of the Blood and the Blood-vessels in Inflammation,' by T. Wharton Jones, F.R.S.; *Guy's Hospital Reports*, vol. viii; *Clinical Lectures*, by J. H. Bennett, M.D., F.R.S.E.; also Professor Henle, as quoted by Wharton Jones, op. cit.

puscles, on the other hand, implied an alteration in the properties of the blood, viz. an abnormal adhesiveness in the red discs. Determination of blood is thus a purely functional phenomenon, and, like a blush upon the cheek, becomes obliterated after death by the post mortem contractions of the vessels: inflammatory congestion, on the contrary, is the first evidence of organic lesion, and declares itself as distinctly in the dead as in the living, being the most important if not the only sign of the early stages of inflammation discoverable on dissection,[1] as for instance in the case of incipient meningitis mentioned in the Introduction to this paper.

Although determination of blood, as met with in the frog, is thus entirely independent of inflammatory congestion, yet it is of great interest with reference to human inflammation. Dilatation of the arteries is now generally admitted to be the result of the relaxation of their muscular fibres; and that it is a purely passive phenomenon, seems to be absolutely demonstrated by the fact which I have pointed out elsewhere,[2] that after the vessels have been liberated from the control of the nervous system by removal of the spinal cord, they dilate fully if the heart continues to act sufficiently powerfully to distend them with blood, but not otherwise. Recent physiological discovery has shown that the arteries are not singular in being thrown into a state of muscular relaxation through irritation of the parts of the nervous system connected with them, the same being the case with the heart, the intestines, and apparently also with other hollow viscera. In a 'Preliminary Account of an Inquiry into the Functions of the Visceral Nerves', published in the *Proceedings* of this Society,[3] I have given some notice of experiments which seem to show that in the case of the viscera alluded to, the state of relaxation under such circumstances is the result of the more energetic operation of nerves, which, when working more mildly, increase the muscular action of the same organs; the functions of the ganglia specially concerned in regulating the movements of the viscera being exalted by gentle stimulation on the part of the afferent nerves connected with them, but depressed by stronger excitation. In that paper the opinion was expressed, that the same explanation probably applies to the relaxation of the arteries,

[1] Since the reading of the paper, I have pointed out that, in consequence of the persistent fluidity of the blood which continues in the smaller vessels for days after death, the red corpuscles have time to gravitate into dependent parts, and thus give rise to that appearance of post mortem congestion which more or less closely simulates to the naked eye what would have resulted from inflammation during life. See a paper by the author 'On Spontaneous Gangrene from Arteritis and the Causes of Coagulation of the Blood in Diseases of the Blood-vessels', *Edinb. Med. Journal,* April 1858 (page 69 of this volume).

[2] See pp. 27 et seq. of this volume.

[3] Page 87 of this volume. The paper here referred to was written subsequently to the reading of the manuscript of this essay, and this was also the case with the remarks in the text on determination of blood.

in consequence of nervous irritation; the general impression conveyed by the experiments with warm water above related being that arterial contraction was most apt to show itself when the degree of irritation was least, while dilatation was most marked when the stimulus was strongest. I have lately seen a striking illustration of this principle in a very simple experiment, which I was induced to make in consequence of reading a paper recently published by a French author, M. J. Marey.[1] If a blunt-pointed instrument, such as the end of a pair of dissecting forceps, is drawn with gentle pressure along the back of the hand while it is in a state of moderate redness, the blood being driven out of the vessels, a pale streak results, which immediately disappears, in consequence of the return of the blood into the part. In a few seconds, however, a pale stripe, towards a quarter of an inch in breadth, becomes developed at each side of the line along which the instrument passed, that line having now assumed a red colour, if the pressure employed was at all forcible. This is M. Marey's experiment; and there can be no doubt that his interpretation of the secondary paleness is correct, viz. that it depends on reflex arterial contraction. The red line, when it occurs, is evidently due to the direct action of the pressure upon the tissues, being, as M. Marey correctly states, exactly of the same breadth as the instrument used. But I find that if the pressure be made with considerably greater force, so as to be positively painful, while the first white streak appears as before in consequence of the blood being dispelled from the vessels, the secondary paleness does not occur, but, on the contrary, a patch of the adjacent skin, extending for perhaps half an inch on each side, assumes abnormal redness, which lasts for a longer time than the paleness to which the other experiment gives rise. Here, the irritation being severe, the blood vessels are thrown through the medium of the nervous system into a state of muscular relaxation, instead of the contraction which is induced by a more gentle application of the same stimulus.

To return to the consideration of inflammatory congestion. Further light was thrown upon the condition of the blood in the vessels of an irritated part by a series of observations made when the circulation had been arrested by amputation of the limb, or by a ligature round the thigh. This field of inquiry was unexpectedly opened during the course of an experiment made with a view to ascertaining the effects produced by an irritant upon the pigmentary system independently of the circulation, as will be described in the next section. On the 13th of October, 1856, a frog having been killed by destruction of the brain,

[1] *Recherches Hydrauliques sur la Circulation du Sang*, par M. J. Marey. The separate copy of this paper, sent me by the author, does not contain any mention of the Journal in which it was published, so that I am unable to give proper reference to it.

the soft parts of one of the thighs were divided to the bone, and a small piece of mustard was placed on one of the webs of that foot. An hour afterwards, on removing the mustard, I saw to my great surprise that the small area on which it had lain was red to the naked eye, and that its capillaries, examined microscopically, contained abundance of closely packed corpuscles, while in surrounding parts the blood was in the same condition as before the experiment, viz. of pretty healthy aspect. In other words, well-marked inflammatory congestion had been produced by the mustard, and I afterwards found that the same thing occurred in a limb completely severed from the body.[1]

This fact of course completely eliminated variations in the calibre of the vessels and consequent changes in the circulation from among the causes of congestion, and demonstrated conclusively its independence of the central organs of the nervous system. Further, it presented a very good opportunity for studying the state of the blood in healthy and inflamed parts, unaccompanied by the effects of rapid movement. In subsequent similar experiments, it was found that the corpuscles were not brought to the irritated area by anything that indicated a mutual attraction between the former and the latter, but were simply carried along by slight accidental movements of the blood, such as are caused by post mortem contractions of the arteries, and instead of moving with facility, as in other parts, stuck when they arrived in the vessels of the area, in consequence of undue adhesiveness. The accumulation of the corpuscles was never to such an extent as in cases in which the heart was driving the blood through the part, but it affected the arterial and venous branches as well as the capillaries. Thus, if a large vein happened to run through the spot upon which the mustard was placed, it became in time choked with a crimson mass of corpuscles in that part of its extent which lay beneath the mustard; but immediately beyond, in both directions, the blood in it contained no more than the usual proportion of corpuscles, or sometimes considerably less; and these moved freely to and fro when the web was touched, whereas those within the area remained fixed. This proved that the cause of the accumulation of the corpuscles did not reside specially in the capillaries, and also showed distinctly that it could not be explained by mere abnormal adhesiveness of the vascular parietes, which was, I understand, the view entertained by the late Dr. Marshall Hall; for supposing the walls of the vessels to experience such a change, which

[1] Mr. Paget, to whom I mentioned this experiment, has informed me that the fact that stasis may be induced by application of irritant substances to the frog's foot after the arrest of the circulation by ligature of the thigh, had been previously discovered by Dr. H. Weber of Giessen (*Müller's Archiv*, 1852), and that Schuler of Glarus had afterwards ascertained that the same thing occurs in an amputated limb (vide *Würzburg Verhandlungen*, 1854).

seems by no means improbable, this could only lead to encrusting of the lining membrane of such a vein with adhering corpuscles, and not to the occupation of its whole calibre by them, as took place in these cases, unless the corpuscles were themselves also abnormally adhesive.

Another important fact which was brought out by this class of experiments is, that mere quiescence of the blood in the vessels of a healthy part fails to induce aggregation of the red corpuscles, such as occurs in blood outside the body. In the parts which had not been subjected to irritation, the corpuscles exhibited no trace of adhesiveness; and though completely at rest, they were nowhere to be seen grouped together, surface to surface, although in the larger vessels there was abundant space for the occurrence of this phenomenon, which invariably presents itself in freshly drawn frog's blood examined between plates of glass in a sufficiently thick film. On one occasion, when examining the tissues of the web of a frog under chloroform, the limb being kept steady by a string tied tightly round the thigh, so as completely to arrest the circulation, I was particularly struck with the total absence of adhesiveness in the red corpuscles; so much so, that, as the foot had been kept moist without circulation for about three hours, I suspected that it must have imbibed water, which, when mixed with blood outside the body, destroys altogether the adhesiveness of the red corpuscles. This, however, proved to be a mistake; for, having occasion to administer more chloroform, I applied it on a piece of lint of considerable size without taking the usual precaution of protecting the foot from the vapour, and left it so for about a quarter of an hour. On re-examination of the web, the red corpuscles were found to possess much mutual adhesiveness, and in the larger vessels were grouped together into masses, with considerable spaces of clear liquor sanguinis, just as in the best-marked forms of aggregation in frog's blood outside the body. One of these masses was drawn by camera lucida, and is represented in the sketch at page 213, along with the outline of the vessel in which it lay. I afterwards purposely induced a similar change in the blood within the vessels of an amputated limb by means of mustard.[1] Having ascertained that the red corpuscles, though they had been long at rest, were perfectly free from the slightest tendency to aggregation, I suspended, at a little distance from the web, a piece of lint smeared with freshly prepared mustard, so that the pungent vapour of the volatile oil might play upon it; and left it so for about a quarter of an hour, when I found the red discs aggregated, as usually seen in frog's blood outside the body. I then shed some blood from the other leg between two plates of glass, and on carefully sketching and comparing the groups of corpuscles in this specimen and those within the vessels of the irritated

[1] This experiment was performed subsequently to the reading of the paper.

webs, found that their characters were precisely similar.[1] These are examples of what very numerous observations have tended to establish, namely, that on the one hand the red corpuscles in the vessels of a perfectly healthy part are free from adhesiveness ; and on the other hand, the adhesiveness which they acquire in inflammatory congestion, though varying in proportion to the degree of irritation, is never greater than occurs in the blood of a healthy part when withdrawn from the body.

These conclusions, if correct, represent cardinal truths, both in physiology and pathology, implying relations of the tissues to the blood both in health and in disease, such as have never before been demonstrated, or, I believe, even suspected. I was therefore anxious to submit them to further test, particularly as it is by no means easy to estimate the precise degree of adhesiveness possessed by the red corpuscles within the vessels ; and it occurred to me that one means of doing this would be to compare specimens of blood shed from inflamed and healthy parts of the same individual ; for if my deductions were sound, the adhesiveness of the red corpuscles ought to be neither more nor less in the one case than in the other.

With this view I made the following experiments. Having carefully examined the blood of a large frog, drawn from a subcutaneous vein of the abdomen, so as to become quite familar with the appearance of its corpuscles, I applied mustard to the whole surface of one foot till inflammatory congestion had been fully developed in it, and then, amputating both feet at the ankle-joint, squeezed out blood from each upon a glass plate, and carefully examined both specimens, without being able to detect the slightest difference between them. The other experiments with this object were performed on the human subject. In one of these I applied a portion of moistened mustard to the dorsal aspect of the last phalanx of one of my fingers, and retained it there for five hours, with the exception of occasional removal for the purpose of drawing blood for examination. By the conclusion of the time mentioned, the skin on which the mustard had been placed was in a very decided state of inflammation, being red, swollen, and painful, and the redness at one spot disappearing imperfectly on pressure, and returning languidly after its removal. A very minute drop of blood drawn with a fine needle from the surface of the most inflamed part was then compared with a drop of similar size from another finger, but no difference could be detected between them, nor had any been observed in pre-

[1] In performing experiments upon a foot in which the circulation has been arrested, it is important to guard against a deception apt to arise from the direct action of an irritant upon the blood in the vessels. Thus, if a drop of chloroform of considerable size be applied to a web under those circumstances, it will soak in and produce its chemical effects upon the blood, the earliest of which is complete abolition of adhesiveness in the corpuscles.

vious similar comparisons. On another occasion, a friend of mine suffering from intense inflammation of the back of the hand, in consequence of the irritation of offensive pus, permitted me to take blood with a needle from the most severely affected part, and also from one of the fingers, which was healthy. I compared drops from the two sources several times very carefully with each other by means of the microscope, but could discover no difference between them in the adhesiveness of their corpuscles ; as indicated by the time of formation of the rouleaux, their mode of grouping, and the tenacity with which the discs composing them adhered when they were stretched. The results of these experiments appear decidedly confirmatory of the conclusion with reference to which they were instituted.

No mention has been hitherto made of the appearance presented by the colourless corpuscles in an irritated part. It is well known that their numbers, in proportion to the red ones, vary very much in different frogs, and it so happened that in the two on which the first mustard experiments were performed they showed themselves but little ; nor are they at all conspicuous when the circulation has been arrested by ligature ; but in most cases in which irritation is applied to the web while the blood is circulating through it, one of the earliest abnormal appearances is that of white corpuscles adhering in large numbers to the walls of arteries, capillaries, and veins, as first described and accurately figured by Dr. Williams.[1] This remarkable phenomenon, though of itself clear proof of an alteration in the properties of the blood in an irritated part, has, strangely enough, attracted little attention from other observers. It is evidently analogous to the change which the red discs experience under similar circumstances. I find that the account commonly given of the white corpuscles in circulation in the vessels of the frog's web, viz. that they may be seen rolling slowly along the walls of the arteries and veins, and sometimes sticking to them, though intended to apply to the state of health,[2] really describes a condition of a slight amount of irritation, such as is exceedingly apt to be induced by a variety of causes.[3] In perfect health the colourless corpuscles

[1] Vide op. cit.

[2] Mr. Wharton Jones, in describing the healthy circulation in the bat's wing, speaks of the colourless corpuscles as ' rolling or sliding sluggishly along the walls of the vessels ', ' both in arteries and veins.' He also describes, in the following passage, increased adhesiveness as resulting from irritation. ' Towards the end of a protracted sitting, after the web had been much irritated, I have seen, in the venous radicles especially, colourless corpuscles accumulated in great numbers, as we so often see them in the frog,' But no stress is laid on this fact as bearing upon the nature of inflammation (see ' Observations on the State of the Blood and the Blood-vessels in Inflammation,' by T. Wharton Jones, F.R.S., *Medico-Chirurgical Transactions*, vol. xxxvi, 1853). Dr. Williams, supposing that the white corpuscles were always adhesive within the vessels in health, was led to attribute their abnormal accumulation in an irritated part to local fresh formation of those bodies (vide op. cit.).

[3] It has been mentioned in the note to p. 225, that this effect is peculiarly liable to be produced in consequence of the vicinity of the warm hand.

are as free from adhesiveness within the vessels as the red discs, but like them assume that property in a degree proportionate to the amount of irritation to which the part has been subjected. When the irritation has been very slight, the white corpuscles, which are susceptible of much greater adhesiveness than the red (as we learn from examining blood outside the body[1]), acquire some tendency to stick to the vascular parietes, while the red discs still move on in a manner generally regarded as consistent with health, though really lagging slightly behind the liquor sanguinis, and consequently presenting themselves in somewhat abnormal proportion. I have often observed the complete absence of adhesiveness of the white corpuscles within the vessels in health, and have also watched them gradually assume a tendency to adhere, in consequence of repeated mild applications of chloroform to a web in which they previously exhibited no such disposition whatever. As the irritation increases, the vessels become crusted with them often to a remarkable degree, and occasionally large, colourless, agglomerated masses of them, just such as are seen in blood drawn from the body, may be observed to roll along the large veins among the slowly moving and very numerous red discs. I once watched the formation of one of these masses[2] as a delta-like accumulation at the place where a considerable venous branch opened into a main trunk, the calibre of which was nearly entirely occupied by it before it was swept away by the current. As a general rule, the white corpuscles when adhering do not arrest the progress of the red ones, which are often seen to pass through very small intervals among the colourless masses; not unfrequently, however, red corpuscles are stopped in their course and adhere among the white ones, and sometimes, especially in young frogs, capillaries become obstructed throughout their entire length by white corpuscles alone, and when this is the case, they are apt to escape notice from the inconspicuous character of their contents.

The adhesiveness of the white corpuscles, as of the red ones, is limited to the part irritated. A very good example of this presented itself on one occasion when a minute drop of chloroform was applied to a small part of a healthy web so as to induce full dilatation of the arteries and great excess of corpuscles, but without absolute stagnation. It happened that the part affected was supplied with blood by the branches coming from one side of a principal artery; the main trunk being seated just about the limit between the irritated area and the healthy region, the adjacent part of which received supply from the branches of the vessel on the other side. The latter showed no appearance of adhering white corpuscles, nor did the capillaries which were fed by them; but those

[1] See p. 214.

[2] This observation was made subsequently to the reading of the paper.

of the irritated part, though springing from the same trunk, were remarkably encrusted with them from their origin to their minutest ramifications within the area, while the capillaries and veins in the same part were similarly affected. This striking appearance continued for hours after the chloroform had been applied, successive fully formed white corpuscles adhering as they flowed in from the trunk, being evidently affected secondarily to the change induced by the chloroform in the tissues of the web.

Thus the affection of the white corpuscles of the blood in an irritated part is in all respects strictly parallel to that of the red discs, while the greater adhesiveness of which the former are capable, renders the facts regarding them more obvious and unmistakable.

Being desirous to verify the results derived from the frog by observations upon mammalia, in which the aggregation of the red corpuscles assumes a much more striking appearance, I examined the wings of two small bats. In the first specimen, the corpuscles, both red and white, exhibited decided adhesiveness within the vessels, the web being apparently in a state of irritation from injuries which the animal had sustained. In the other there was also some adhesiveness in the part that first met my eye, the red discs tending to aggregate into rouleaux, and giving a lumpy aspect to the somewhat dark streams in the larger vessels : but turning to another place, I found the blood there of pale tint and perfectly homogeneous aspect ; nor could I detect by a careful search any evidence of a tendency on the part of the white corpuscles to stick to the vascular parietes. It happened that there was complete absence of flow in one artery and concomitant vein of considerable size, yet not a rouleau was to be seen either in them or in any of their branches. On the contrary, the red discs lay at about equal distances from each other, uniformly distributed throughout the calibre of the vessels ; and this state of things remained unchanged during about a quarter of an hour, in which I continued to observe them in their perfectly quiescent condition. On examination of some blood from the heart of this bat shortly after, the red corpuscles exhibited a very remarkable degree of adhesiveness, such as I had never seen in human blood,[1] presenting a glaring contrast with their state within the vessels.[2]

[1] The remarkable adhesiveness of the red corpuscles of the blood of this bat, when withdrawn from the body, has been particularly described in Section I, p. 213.

[2] Mr. Wharton Jones, in the paper before referred to, describes the red discs as aggregating within the vessels of the healthy bat's wing, when their movement is arrested from any cause, in the same manner as in blood removed from the body. Vide *Med.-Chir. Trans.*, loc. cit. I suspect that the pressure of the plate of thin glass employed in order to bring the necessarily high powers of the microscope to bear upon the object is apt to irritate the web and give rise to a degree of congestion, characterized by a tendency to aggregation on the part of the red discs and adhesion of the colourless corpuscles to the walls of the vessels. I have observed that results of irritation have shown themselves in the web

Thus we may, I think, regard it as fully established, that, in mammalia as well as in amphibia, both the red discs and the colourless globules of the blood are completely free from adhesiveness within the vessels of a perfectly healthy part, but that when the tissues have suffered from irritation, both kinds of corpuscles assume, in proportion to the severity of the affection, a degree of that tendency to stick to one another and to neighbouring objects which they possess when withdrawn from the body, and consequently experience obstruction to their progress through the minute vessels.

And here I cannot avoid remarking, that this principle explains, if it does not altogether reconcile, the discordant opinions of physiologists regarding the causes of the circulation. It shows that while there is, as we have before seen,[1] strong ground for agreeing with those who hold that the flow of the blood is due simply to the contractions of the heart, aided, in animals with valved veins, by the actions of the muscles, the respiratory movements, and, in the case of the bat's wing, by rhythmical venous contractions ; yet there is also much truth in the view of those who maintain that the tissues of a part, independently of any change of calibre in the vessels, exercise a great influence upon the progress of the blood through the capillaries. For though the tissues do not, as has been hitherto supposed by the latter class of authorities, actively promote the circulation, yet their healthy condition is none the less necessary to it, being essential to the fitness of the blood for transmission by the heart through the minute vessels.

It is an interesting question, whether the freedom of the corpuscles from adhesiveness in health is due to some active operation of the tissues upon the vital fluid, or whether their adhesiveness in an inflamed part or outside the body is the result of a prejudicial influence exerted upon the blood by the irritated tissues, or by the objects of the external world with which it comes in contact when shed. The fact that the non-adhesiveness of the corpuscles within the vessels continues in an amputated limb, shows that it is independent of the central organs of the nervous system, and probably too of any nutritive actions going on in the tissues. Also, if the latter were concerned in its production, we should expect to find the corpuscles adhesive in the large arteries and veins of the webs, since it is doubtless chiefly in the capillaries that the mutual interchanges take place between the blood and the solid elements of the body. It may be difficult to obtain further evidence upon this point, but some light may be thrown upon it by the consideration of the causes of the coagulation of the blood, which seems to be a closely allied subject.

of the frog when I have used a plate of thin glass in the same manner as with the bat, for the purpose of applying a high power to the pigmentary tissue.

[1] See p. 220.

I have shown elsewhere,[1] that in mammalia, as well as in amphibia, the blood remains fluid for days in the veins of an amputated healthy limb, though retaining its property of coagulating when shed.[2] Its fluidity within the vessels is unaffected by free admixture of the atmosphere with it. For example, seven hours after injecting air into the veins of an amputated sheep's foot, I found the frothy mixture contained in the vessels still quite fluid; and the blood which formed the bubbles, coagulated when shed. Again, a human leg having been amputated above the knee, I pressed out the blood from about an inch of the open mouth of the popliteal vein, and covered the raw surface lightly with a damp cloth, so as to guard against drying of the blood, or of the walls of the vessel in contact with it. After the lapse of twenty-four hours, the vessel was still patulous; but the blood, though it had been so long freely exposed to the influence of the air, continued perfectly fluid. Further, if a vein in an amputated sheep's foot is simply wounded, no clot forms except at the seat of wound. If, however, a portion of any ordinary solid matter, such as a fragment of glass, a bit of clean wax, a hair, a needle, or a piece of fine silver wire, be introduced into such a vein, a deposit of fibrine takes place after some minutes upon the foreign body,[3] followed by coagulation of the blood in that particular part of the vessel; the coagulum, however, never adhering to the vein, except at the lips of the wound.[4] This shows that an ordinary solid possesses an attraction for

[1] See a paper by the author 'On Spontaneous Gangrene from Arteritis and the Causes of Coagulation of the Blood in Diseases of the Blood-vessels', *Edinburgh Medical Journal*, April 1858 (p. 69 of this volume). The observations there recorded, and also the others mentioned in the text with regard to coagulation, have been made since the reading of the original manuscript.

[2] The blood coagulates more slowly the later it is examined after death or amputation, and finally becomes altogether incapable of the process. The time when this occurs differs in different cases. Thus, in the foot of the sheep I have seen coagulation take place, though slowly, on the sixth day; but in the human subject on one occasion I found the blood remain permanently fluid when shed within forty-eight hours of death, though in another instance at the same period a soft clot formed in about half an hour.

[3] These facts, ascertained in November 1858, have considerably modified the views expressed in the paper above referred to.

[4] From what has been stated in the text, it is evident that the ammonia theory of Dr. B. W. Richardson does not account for the fluidity or coagulation of the blood within the vessels. But the facts mentioned by that gentleman in the valuable essay which has gained the last Astley Cooper prize, and also my own experience [see the paper before referred to], have convinced me that a certain amount of the volatile alkali does exist in freshly drawn blood, and that it has the effect of retarding the process of coagulation. This principle must be borne in mind in all experiments upon this subject, in order to understand circumstances which would otherwise be inexplicable. Thus, if the foot of a sheep be obtained with the blood retained in the vessels by a bandage applied before the death of the animal, and, after reflexion of the skin, a needle be introduced into a vein by a free opening made by the scissors, a deposit of fibrine will be found upon it in perhaps five minutes; but if the needle be pushed through the coats of such a vein, so as to introduce it without previous wound of the vessel, and allow little opportunity for escape of ammonia, the deposit will not take place for a quarter of an hour or more. Again, the blood obtained by wounding a vein immediately after reflecting the skin, within the first few hours after the death of the animal, takes a much longer time to coagulate than the blood shed from the same vessel after the lapse of half an hour or so; doubtless in consequence of escape of ammonia

the particles of the fibrine, such as is not exercised by the walls of the vessels; or, in other words, that the vascular parietes differ from all ordinary solid substances in being destitute of attraction for that element of the liquor sanguinis.

The blood-vessels are not the only constituents of the animal body which have these remarkable relations to the blood. If the integument of a sheep's foot be partially reflected, and one of the subcutaneous veins immediately wounded, so as to let some blood run into the angle between the skin and the rest of the limb, before any drying of the tissues has occurred, care being taken that no hairs or other solid matters have been introduced, this blood will remain in whole or in part fluid for half an hour or more; whereas, if blood from the same vessel be placed in contact with any ordinary solid, whether on the foot or elsewhere, it will coagulate in perhaps five minutes.[1] This is sufficient proof that the subcutaneous cellular tissue resembles the lining membrane of the vessels in its conduct towards the blood. The long time during which blood has been observed to remain fluid but coagulable in the tunica vaginalis, seems to show that serous membranes are similarly circumstanced: and it appears probable that the same may be the case with other tissues.

But though some of the facts above mentioned furnish clear evidence that ordinary solid matter induces coagulation by an attractive agency, it by no means follows that the tissues are necessarily merely neutral in their conduct towards the blood in this matter. It is quite possible that they may exert an active influence upon it, in consequence of which the particles of fibrine may experience a mutual repulsion, in the same way as would seem to be the case with the pigment-granules of the chromatophorous cells of the frog during the process of diffusion,[2] Indeed some such hypothesis seems almost necessary

having occurred in the interval. This circumstance seems to prove that the ammonia is free in the blood in its normal condition within the vessels, and not merely liberated during the process of coagulation; for it is to be remembered that the mere wounding of a vein in no way interferes with the fluidity of the blood in it, except at the wound.

[1] After the blood has lain for some time in the angle between the skin and the limb, it coagulates, if removed from it, much more rapidly than blood freshly shed from a vessel. Thus, in one case, blood let out from a vein was part of it placed at once on a glass plate, and part allowed to run into the angle between the skin and limb. That on the glass plate was not completely coagulated for ten minutes; but that in the other situation, having been left for twenty minutes, and then transferred to the plate, was a consistent clot within six seconds, indeed as soon as I could examine it. This fact seems to me to throw great light upon the subject of coagulation. The sudden transition from perfect fluidity to a coagulum can only be explained, I conceive, on the hypothesis that the ammonia had almost all escaped while the blood lay in the angle; yet this escape had not caused coagulation. Hence it seems to follow, that ammonia is in no way essential to the fluidity of the blood while it is surrounded by healthy tissues. Another point, which the simple experiments upon the sheep's foot show clearly, is that a certain amount of ammonia in the blood will retard without preventing the deposit of fibrine upon a needle or other ordinary solid introduced into the vessels; and it appears very doubtful whether healthy blood ever contains sufficient ammonia to prevent such an occurrence.

[2] See p. 56 of this volume.

in order to explain the remarkable fact, that the blood coagulates within a few hours of death in the cavities of the heart and great venous trunks, though it retains its fluidity for days in the smaller vessels. Thus in the human subject twenty-four hours after death I have found clots in the heart and larger veins, including the upper parts of the axillary and femoral trunks, but fluid blood in the lower parts of those vessels and all their branches in the limbs. It seemed possible at first that this difference might depend on the position of the great vessels in the thorax and abdomen, where decomposition begins earlier than in the limbs. But this proved not to be the case ; for in a horse twelve hours after it had been killed, I found the blood fluid in the intercostal and small cardiac veins, though coagulated in the vena cava and the coronary vein of the heart, which is in that animal of very large size. There being no reason to suppose the walls of the larger vessels differently constituted from those of the smaller ones, or more liable to undergo post mortem changes, the natural interpretation of these facts seems to be that the blood has, even within the body, a certain tendency to coagulation, counteracted by an influence exerted upon it by the containing tissues, which, operating to less advantage the larger the mass of the fluid acted on, fail, at least after death, to prevent it from following its natural course in vessels of a certain magnitude. Again, if we suppose that the tissues are merely passive with regard to the blood, it seems difficult to understand the rapid solidification of a large quantity shed into a cup. For we have seen that mere exposure to the atmosphere will not account for the fact ; while at the same time the experiments upon the sheep's foot indicate that an ordinary solid has but a very limited range of operation upon the surrounding blood,[1] and that the clot which it induces does not propagate itself to more distant parts ; so that the central portions of such a mass of blood should remain fluid, unless we admit that, when shed from the vessels, it is liberated from an influence which previously kept in check a spontaneous proneness to coagulation. Hence it seems likely that a foreign solid introduced into a vein acts not by creating a disposition to aggregate on the part of the fibrine, but by increasing a pre-existing tendency to it (as a thread induces the crystallization of sugar-candy), exalting the mutual attraction

[1] I find that if a needle is introduced into a vessel and removed after the expiration of about two minutes, before any deposit of fibrine has yet occurred upon it, a certain amount of coagulation nevertheless takes place afterwards in that particular part of the vessel in which the needle had lain. This is a curious circumstance, indicating that an impression leading to coagulation is produced upon the blood by contact with an ordinary solid for a shorter time than causes, during its presence, any visible solidification. The clot, however, is very slow in forming and very incomplete, so that such cases cannot be compared with the perfect and rapid coagulation of a large mass of blood outside the body. Indeed, when blood is drawn into a large cup, a great deal of it never touches the side (the ordinary solid) even for an instant.

of its particles to a degree which overcomes a counteracting agency on the part of the tissues.

Further inquiry will, in all probability, throw clearer light upon this subject, but in the meantime the facts already known furnish to the unaided senses indisputable proof of the fundamental principle to which we were led by microscopical observation, viz. that the tissues through which the blood flows have, when healthy, special relations to the vital fluid, by virtue of which it is maintained in a fit state for transmission through the vessels. Further, the differences of adhesiveness in the corpuscles according as the blood is surrounded by healthy tissues or ordinary matter, can now be no longer matter of surprise, knowing as we do the alterations which take place in the chemical condition of the liquor sanguinis in consequence of such changes of circumstances, and also the great effect produced upon the adhesiveness of the red discs in blood outside the body by slight variations in the quality of the plasma.[1]

The freedom from attraction for the fibrine, if not the actual repulsion of it, on the part of the walls of healthy blood-vessels, seems to explain the well-known fact in pathology, that when healthy capillaries are subjected to abnormal pressure in consequence of venous obstruction, the fluid squeezed through their parietes consists almost exclusively of serum ; the fibrine being apparently excluded from their pores as liquid mercury is from those of flannel, or any other texture composed of a material destitute of attraction for it.

From the speedy coagulation of lymph effused into the interstices of inflamed organs or upon inflamed serous surfaces, compared with the length of time that blood has been known to remain fluid after being poured out into such situations in a state of health, and also from the deposition of fibrine which occurs at an early period upon the lining membrane of the vessels in arteritis or phlebitis, whether in the limited inflammation which results from the application of a ligature, or in the more extensive affection which is apt to occur spontaneously, it would appear that the liquor sanguinis, like the corpuscles, tends to comport itself near inflamed tissues as if in the vicinity of ordinary solid substances. It is true that coagulation is not observed to occur in the vessels of the frog's web after the application of irritants ; but this is accounted for by the length of time required for the occurrence of the process within the vessels, the liquor sanguinis passing on into healthy regions, leaving the adhesive corpuscles behind it. Adhesiveness of corpuscles may, however, come on in circumstances which admit of permanent fluidity of the blood. Thus if a cat be killed without haemorrhage, and one of the jugular veins be exposed and tied in two places, and the animal be then suspended by the head

[1] See Section I, p. 214.

so that the vein may be vertical in position, the upper part of the venous compartment included between the ligatures will within a very few minutes become colourless in consequence of rapid subsidence of the red corpuscles, implying that they are already closely aggregated, although, if the skin be carefully replaced so as to prevent drying of the tissues, the blood will remain fluid in that part of the vein for many hours. Whether the adhesiveness of the corpuscles in this case depend on a post mortem change in the vessels, or whether it is merely the result of the large size of the vein preventing the tissues from acting effectually on the blood, remains to be determined ; but such a fact seems to prove that a higher grade of vital activity, so to speak, is required to prevent adhesiveness of corpuscles than to maintain the fluidity of the blood. Hence it is probable that, even if the blood were at rest in the vessels of a part, a stronger degree of irritation would be required in order to determine coagulation than would suffice to induce adhesiveness of the corpuscles, which seems to be a more sensitive test of a deviation of the tissues from the standard of health. I have, however, ascertained, by experiments upon the amputated sheep's foot, that if caustic ammonia is applied freely to a part of a vein after pressing the blood out of it, and the blood allowed to return when the ammoniacal odour has passed off, coagulation takes place in the portion of the vessel which has been so treated, although the chemical action of ammonia, if any of it remained in the tissues, would tend to prevent or check coagulation.[1] I have also found a similar local clot form, though more slowly, after merely pinching a piece of a vein.

The principal results obtained in this section may be summed up as follows :—

The effects produced upon the circulation by the application of an irritant to a vascular part are twofold, consequent upon two primary changes in the tissues, which, though often concomitant, are entirely independent both in nature and mode of production. One of these is dilatation of the arteries (commonly preceded by a brief period of contraction), giving rise, in proportion to the increase of calibre, to more free flow through the capillaries, the blood remaining unaffected, except in the rate of its progress. This purely functional phenomenon is developed indirectly through the medium of the nervous system, being not limited to the part acted on by the irritant, but implicating a surrounding area of greater or less extent. The other change is the result of the direct operation of the irritating agent upon the tissues, which experience some alteration, in consequence of which the blood in their vicinity becomes impaired, losing the properties which characterize it while within a healthy part, and

[1] See the paper 'On Spontaneous Gangrene', &c., before referred to.

which render it fit for transmission through the vessels, and assuming those which it exhibits when removed from the body and placed in contact with ordinary solid matter. The first indication of this disorder of the vital fluid is, that its corpuscles, both red and white, acquire some degree of adhesiveness, which makes them prone to stick to one another and to the vascular parietes, and, lagging behind the liquor sanguinis, to accumulate in abnormal numbers in the minute vessels. This adhesiveness may exist, in proportion to the severity of the affection, in any degree, from that which merely gives rise to a very slight preponderance of the corpuscular elements of the blood in the part, up to that which induces complete obstruction of the capillaries ; and when the irritation has been very severe, the liquor sanguinis also shows signs of participation in the lesion by a tendency to solidification of the fibrine.

SECTION IV

On the Effects of Irritants upon the Tissues.

The object of the present section is to inquire into the nature of that primary change which we have seen to be produced in the tissues by the direct action of irritants upon them.

The conclusion already arrived at, that blood flowing through an irritated part approaches more and more nearly, in proportion to the intensity of the affection, the condition which it assumes when separated from the living body, naturally leads us to infer that the tissues concerned are in some degree approximated to the state of ordinary matter, or, in other words, have suffered a diminution of power to discharge the offices peculiar to them as components of the healthy animal frame.

This inference is strongly supported by considering what common effect is likely to be produced upon the tissues of the frog's web by all the various agents known to cause inflammatory congestion. To take first the case of mechanical violence. A forcible pinch of the delicate web seems likely, *a priori*, to impair its powers ; for if the lesion be sufficiently severe, complete death of the part will result. An elevated temperature proves equally destructive if carried far enough ; and its operation to a degree just short of this, while it produces congestion, can hardly fail to cause diminished vigour in the tissues. So also powerful chemical agents, if used cautiously, give rise to inflammation ; but if otherwise, kill the part they act on. Even the pungent irritants which do not exert much chemical action, seem to benumb the energies of the spot to which they are applied. Thus a morsel of capsicum placed on the tip of the tongue speedily produces numbness there, and a piece of mustard lying on the finger for an hour or two dulls the sensibility of the skin. Chloroform, too, while it very readily induces stagnation followed by vesication in the frog's web, is an agent which appears likely to benumb the vital energies. If a small frog be put into a bottle of water highly charged with carbonic acid, and removed from it some time after all motion of the limbs has ceased, it will be found that, though the heart is still beating, the blood-vessels of the webs are loaded with stagnant corpuscles. After a while, however, resolution will take place, and some time later the animal will regain its consciousness. Here it appears probable that the carbonic acid, poisoning the web as well as the brain, paralyses for a time the functional activity of both ; and that the return of the circulation, like the recovery of the cerebral functions, depends on a restoration of the dormant faculties of the affected tissues.

Perhaps the most instructive case is that of the galvanic shock, which the following circumstances first showed me to be capable of causing inflammatory congestion. Being desirous of ascertaining the effects of galvanism upon the cutaneous pigmentary system, I applied the poles of a battery in rather powerful action to the skin of the head of a frog, when, the shock affecting the brain, the animal was stunned and lay perfectly motionless. This state of things being favourable for pursuing my inquiry by aid of the microscope, I drew down one of the passive limbs, and having placed the foot under the instrument, arranged the fine platinum-wire extremities of the poles at a short distance from one another at opposite sides of one of the webs, so that the current might pass through a part in the field of view, the circulation meanwhile remaining healthy. I now completed the circuit of the battery, when the leg became instantly drawn up by reflex action ; yet on re-examination of the web, I found that, momentary as the shock had been, the part through which it had passed had become affected with intense inflammatory congestion, gradually shading off towards the healthy condition, which existed at a little distance. After about a quarter of an hour resolution of the confused mass of stagnant corpuscles occurred, and shortly after this the creature regained the power of voluntary motion. I afterwards repeated the experiment, both upon the same animal and upon another specimen, and always with the same results ; and I particularly observed in one case that the white corpuscles were affected with great adhesiveness in the congested region.

With regard to the manner in which the abnormal condition of the blood was brought about in these cases, it has been already mentioned in Section I that the galvanic current produces no increase of the adhesiveness of the red corpuscles of blood outside the body ; but after what has been stated in the last section, the reader will see no reason to think such an effect likely. It may, however, seem not improbable that the galvanic shock might, by its direct action upon the blood within the vessels, reduce it to the same condition as if removed from the body. But that this was not really the cause of the congestion, was clear from the fact that in the parts less intensely affected, where the corpuscles still moved slowly though possessed of considerable adhesiveness, the same condition continued long after all the blood which was in the vessels when the shock was transmitted had passed away. In this case, therefore, as in all the others which we have considered, the blood was affected secondarily to the tissues. This being established, the natural interpretation of these experiments appears to be, that the portion of the web affected was, as it were, stunned by the shock, and its functions suspended like those of the brain ; the resolution of the inflammation, like the return of volition, depending on recovery of function on the part of the tissues concerned.

From such considerations as these, it appears that all those agents which produce inflammatory congestion when applied to the web, though differing widely in their nature, agree in having a tendency to inflict lesion upon the tissues and impair their functional activity.

But powerful as are the arguments thus obtained by inference, it is very desirable to confirm them by direct observation, and it fortunately happens that the cutaneous pigmentary system of the frog is a tissue which discharges functions very apparent to the eye, so that it is easy to trace their modifications under the influence of irritation.

In the first experiment with mustard described in the last section (performed September 29, 1856), the space on which the irritant had acted presented a very striking difference from the rest of the web in the appearance of the pigment, which in healthy parts was in the form of small roundish black dots ; while in the mustard area, and accurately corresponding to the extent of stagnation in the capillaries, each spot was extended to a stellate figure.

I thus became for the first time aware that the pigment is capable of variations, and my attention having been directed to the subject, I soon found that similar changes occur spontaneously, and give rise to alterations in the colour of the skin, which is paler in proportion as the colouring matter is more completely collected into round spots. For some weeks I supposed myself to have been the first discoverer of this curious fact, till I was referred by Dr. Sharpey to the recent labours of the Germans on the subject. They, however, as I afterwards found, had taken an entirely erroneous view of the phenomenon, attributing the round form of the masses of pigment to contraction of the branching offsets of stellate cells ; whereas it turned out that the chromatophorous cells do not alter in form, but that the colourless fluid and dark molecules which constitute their contents are capable of remarkable variations in relative distribution, the molecules being sometimes all congregated in the central parts of the cells, the offsets containing merely invisible fluid, while at other times the colouring particles are diffused throughout their complicated and delicate branches ; and between these extremes any intermediate condition may be assumed. It further appeared that concentration of pigment takes place in obedience to nervous influence, while diffusion, though also an active vital process, tends to occur when the pigment-cells are liberated from the action of the nerves. But for further particulars on this subject, I beg to refer the reader to a previous paper in this volume.[1]

The contrast between the pigment in the area on which the mustard had acted and that of surrounding parts in the case last alluded to, at once struck me as probably the result of a direct action exercised upon the tissues by the irritant. It seemed possible, however, that it might be a secondary effect of the state of the blood in the congested vessels ; and in order to ascertain which was the truth, I performed, on the 14th of October the following experiment :—

Having cut out a piece of the web of a healthy frog, I placed a small portion of mustard upon its centre when all the blood had escaped from it. After a while the spots of pigment seen through the thin margin of the mustard, presented a stellate form, while in the rest of the piece they were still of a rounded figure. Hence it was clear that the change in the disposition of the pigment was the result of the direct action of the mustard upon the tissues of the web.

A new field of investigation was thus opened before me, promising to throw great light upon the nature of inflammation.

To explain the effects of irritants upon the pigmentary tissue proved, however, to be a matter of considerable difficulty. Tincture of cantharides and croton oil, which happened to be among the first substances which I employed with reference to this subject, resembled mustard in causing diffusion of the pigment. Taking, in the first instance, the same view of this change as the German authorities, I attributed it to the relaxation of contractile cells, and regarded its occurrence, in consequence of irritation, as an indication of loss of power in the tissues, a view which was in harmony with the nature of the derangement of the blood in a congested part. Croton oil, curiously enough, acted very slowly on the web, not producing any change on either pigment or blood for an hour or more : also its effects appeared inconsistent with my theory ; for while it ultimately gave rise to diffusion of the pigment to even a greater extent than I had seen occur with mustard, yet it induced only comparatively

[1] See pp. 48 et seq.

slight appearances of congestion. Chloroform also seemed at first still more anomalous in its operation, though in the opposite way; for though it was pre-eminently potent in inducing congestion, it caused no alteration whatever in the appearance of the pigment, whether mildly or strongly applied.

Afterwards, as the true nature of the pigmentary functions became unveiled, and further facts were developed, these difficulties were completely cleared away. The first step towards their solution was made in an experiment with ammonia. A frog being placed under chloroform, I covered the whole of the foot with sweet oil, except a small area in one of the webs, the pigment being in the stellate condition, i.e. about midway between perfect concentration and full diffusion. An assistant then held at a short distance above it a piece of lint soaked in the strongest liquor ammoniae, so that its pungent alkaline vapour might play upon the exposed area, while the rest of the foot was protected by the oil. This having been continued for a few seconds, accumulation of corpuscles and stagnation occurred in the vessels of the area, without any change in the appearance of the pigment. After a while, however, the creature happened to grow pale, and, in the web generally, the pigment became completely concentrated so as to assume the dotted aspect, but in the part which was the seat of congestion it remained stellate as before. Hence it appeared that though the ammonia did not cause any change in the distribution of the pigment, it had in reality produced a great effect upon the chromatophorous cells, which, in the area exposed to its influence, had been deprived of the power of concentration by the mildest degree of action of the alkali that sufficed to induce stagnation of the blood. On examination of the web about four hours later, resolution of the stagnation was found to have taken place, though there was still some excess of corpuscles, with marked adhesiveness of the colourless ones in the vessels of the ammonia area. The creature was now released for the night. Next morning the integument was in the opposite extreme of colour, being almost black, and the pigment had the reticular appearance, being fully diffused throughout the whole web, except the central part of the ammonia area, where it retained the same stellate condition as the day before. Hence it appeared probable that the diffusive power, as well as the concentrating, had been paralysed by the ammonia, but had been recovered in all the area except the part that was likely to be the last to regain its functions. To ascertain whether the concentrating power had also been regained, I killed the frog and amputated the leg; soon after which the usual post mortem concentration took place completely in the web generally, while in the central part of the area the medium state was still retained, and in the rest of its extent concentration considerably beyond the medium state, but short of the full degree, supervened, showing that recovery of function had taken place to a considerable extent, but was not yet quite complete.

I now felt little doubt that chloroform also possessed the power of arresting the pigmentary functions ; but in order to prove the fact I killed a dark frog, and placed one of its legs in that fluid for half a minute, and then wrapped both it and the other leg in damp lint. After some hours the limb which had not been treated with chloroform was quite pale, while the other, having lost the faculty of post mortem concentration, remained as dark as before. The appearance presented by the pigment in the two feet is shown in Plate III (page 68), Figs. 1 and 2.

Mechanical violence proved similar in its effects on the pigment, which, in the area pinched, retained the same appearance as before, except that in parts where the pressure operated most severely the cells seemed sometimes to have suffered rupture. Fig. 2, Plate V is a camera-lucida sketch of part of a spot which had been compressed by means of padded forceps, with an adjoining uninjured portion of the web. The pigment was fully diffused before the experiment was performed, and remained so afterwards in the area squeezed, while it became concentrated elsewhere, and this was the condition of things when the drawing was made. The concomitant differences in tint between the blood in the affected and the sound parts in consequence of the accumulation of closely packed red discs in the former, are also strikingly shown in the sketch.[1]

The galvanic shock, too, produced no effect apparent to the eye upon the pigment of the parts in which it caused stagnation of the blood, but experiments afterwards made showed me that, like ammonia, it exerted a paralysing agency both upon the concentrating and the diffusive powers ; and the same results ensued on the application of dry heat in the cases mentioned in the last section.

From these and other similar facts it appeared that mustard, croton oil, and cantharides are exceptional as regards the diffusion to which they give rise, the usual course being that irritants, when applied so as to produce stagnation of the blood, suspend at the same time both the functions of the pigment-cells.

It afterwards turned out that mustard was, in reality, no exception to this general rule. Subsequent experiments showed that diffusion takes place

[1] Much more gentle pressure, if long continued, may give rise to similar results, as I happened to notice in the following manner. Being desirous of watching the process of post mortem concentration of the pigment, I amputated a leg of a dark frog, and, having stretched out the foot over a glass plate, put a small piece of thin glass upon part of one of the webs, and applied a high power of the microscope to it. I was disappointed to find, however, that the change I wished to observe did not take place ; but on looking at other parts of the web, found that immediately beyond the edge of the slip of thin glass the pigment was on all sides considerably concentrated, although remaining fully diffused where the glass covered it ; an effect which I could attribute only to the gentle squeezing to which the two plates subjected the part of the web that lay between them.

to very different degrees in different instances under the action of this substance, but that in all cases, after reaching a certain point, it becomes incapable of advancing further in the irritated part, however much it may increase in the body generally, in case of the animal changing to a darker colour. These differences depend partly upon the strength of the mustard, the diffusion being least when the irritant is most potent. Thus, on one occasion, when a solution of the volatile oil in spirit of wine was applied to a web in which the pigment was fully concentrated, congestion was very rapidly developed, without any alteration in the appearance of the chromatophorous cells. That the diffusion is in inverse proportion to the energy with which the mustard acts, was well illustrated by the experiment which furnished the drawing given in Plate V, Fig. 1.[1] In that case, a frog having been prepared in the manner mentioned in the note to p. 32, a portion of very strong mustard was placed upon the middle of one of the webs, the pigment being in the stellate condition, such as is seen on the left-hand side of the sketch, which represents a part of the edge of the spot to which the irritant was applied, together with an adjoining portion of the web. Shortly after this had been done, I noticed that the pigment was in a state of full diffusion in a ring round about the opaque mass, producing the reticular appearance shown in the stripe down the middle of the sketch. I had in a previous case seen a similar ring become affected with congestion, when a portion of mustard had been applied for a long time, in consequence of the pungent vapour of the volatile oil playing upon the neighbouring parts of the web, and there could be no doubt that the effect on the pigment in the present instance was due to the same cause ; but in the latter no material change was as yet visible in the blood except close to the edge of the mustard, where the corpuscles were seen to be abnormally adhesive. After the lapse of about an hour, the area on which the irritant had lain being examined, was found to be the seat of the most intense inflammatory congestion, indicated in the drawing by the crimson colour of the vessels, but the pigment there had experienced only an exceedingly slight degree of diffusion, being, in fact, almost exactly in the same state as at the commencement of the experiment. Thus the vapour of the volatile oil, though operating too mildly to cause inflammatory congestion, nevertheless induced the highest possible degree of pigmentary diffusion ; but the mustard, where it lay actually in contact with the web, and acted energetically upon it, arrested that very process of diffusion to which its gentler operation gives rise.

In the progress of the case it happened that the animal changed from the medium tint which it had at first to a very pale colour, the pigment, in the web generally, assuming the dotted condition depicted on the right-hand side of

[1] This experiment was performed subsequently to the reading of the paper.

the drawing. Yet many hours after the mustard had been removed, the pigment on which it had acted retained its stellate disposition, and the reticular appearance in the surrounding ring also remained unchanged, showing that the power of concentration had been permanently lost in those parts, and affording a favourable opportunity for obtaining by means of the camera lucida a delineation of the medium, and both extreme conditions of the pigment in the same web. Next day the experiment was rendered still more instructive by the skin becoming excessively dark, the pigment undergoing full diffusion in the healthy parts of the web, so that the contrast between the ring about the congested area and the surrounding regions no longer existed : yet the stellate condition was still maintained where the mustard had lain, showing that it had suspended the faculty of diffusion no less than that of concentration.

Croton oil now no longer seemed anomalous in its operation. Its curiously slow action upon the frog is comparable to the mild influence of the vapour of mustard, and the slight amount of inflammatory appearance which I had sometimes observed in a part where it had caused a great degree of pigmentary diffusion, is strictly analogous to the healthy state of the circulation in the reticular ring round the congested area in the last experiment.

Cantharides also presents a parallel case. Its action is even more slow than that of croton oil ; and on referring to notes taken at an early period in this investigation, I find that in one instance, when two hours and a half had elapsed after the application of a small drop of the tincture to the web, though diffusion of the pigment had become apparent in the area on which it had acted, no change of the blood had yet been observed ; and an hour and a half later, the red corpuscles, though abnormally adhesive as compared with those in surrounding parts of the web, were still moving slowly through the vessels.

Hence it appears that diffusion of the pigment may be produced by either of these three substances without the blood undergoing any material derangement, and therefore that its occurrence under their influence is to a great extent, if not entirely, independent of the inflammatory process. On the other hand, it has been demonstrated, as regards mustard, that when stagnation of the blood has been developed through its action, the state of the pigment-cells is the same as is induced by irritants generally, viz. a complete suspension of functional activity ; and, from analogy, we may be pretty sure that this is also true of croton oil and cantharides, although their slow operation renders it difficult to obtain absolute proof upon the point.

In a physiological point of view, it is an interesting question, what is the cause of the diffusion of the pigment induced by these three irritants. I have shown elsewhere[1] that concentration is the invariable result of the action of the nerves upon the chromatophorous cells, and that diffusion takes place whenever they are liberated from nervous influence. Also in the tree-frog of the Continent, which is much more liable to changes in the colour of the integument, in consequence of direct irritation, than our own species, the invariable experience of the German observers was, that concentration followed the application of a local stimulus, while secondary diffusion sometimes occurred in the irritated spot, depending apparently upon exhaustion.[2] From these facts, diffusion ensuing on irritation cannot well be regarded as an increased action excited by the stimulus, but rather as an evidence of diminished vigour. With croton oil and cantharides, which have not an irritating vapour, the diffusion is exactly limited to the extent of the irritant, showing that it is due to a direct action on the tissues; and the most probable explanation of its occurrence appears to be that mustard, croton oil, and cantharides have the peculiarity among irritants of affecting the nerves of the pigment-cells in the part they act on, somewhat more rapidly than the cells themselves, and, paralysing the former while the latter still retain their powers more or less intact, permit diffusion to go on unrestrained by nervous influence, till the further operation of the irritant completely suspends the pigmentary functions. It may be objected to this view, that diffusion occurs on the application of these substances to an amputated limb, but, from evidence given elsewhere,[3] it is probable that the pigment-cells possess a local nervous apparatus, on which the occurrence and maintenance of post mortem concentration depend, and the paralysis of which, while the pigment-cells retain their powers, would give rise to diffusion in an amputated limb. Be this as it may, the fact that the state of full diffusion continued in the ring around the congested area in the last mustard experiment for hours after the irritant had been removed, although, during that time, complete concentration occurred in the web generally, is pretty clear evidence that the pigment-cells in that part had not merely been stimulated to increased action (for in that case they would have returned to their former condition soon after the stimulus had ceased to operate), but had suffered a loss of the faculty of concentration. Whether the loss of power resided in the nerves of the pigment-cells, or in those cells themselves, is a matter of indifference as regards the objects of the present inquiry; the important fact being that an action of the mustard so mild as to give rise to little or no derangement of the blood, nevertheless produced a certain degree of loss of power in the part on which it operated. There can be no doubt that the same principles apply to the cases of croton oil and cantharides; and thus the diffusion caused by these

[1] See the paper 'On the Pigmentary System', p. 64. [2] See p. 48. [3] See p. 63.

three irritants assumes a high interest, as visible evidence of diminished functional activity accompanying, if not preceding, the earliest approaches to inflammatory congestion in parts which have been subjected to their influence.

With the view of ascertaining the nature of the effect produced on the pigment-cells by the mildest action of chloroform which is capable of causing inflammatory disorder, I ascertained, by repeated experiments, the shortest time in which the vapour of that liquid gave rise to unequivocal signs of a congestive tendency in the web of the living frog; and having found this to be about half a minute, suspended for that period one of the legs of a recently killed dark frog in a vessel, the bottom of which was covered with chloroform, having previously examined the webs microscopically, and found that full diffusion of pigment existed throughout them. The result was that the limb exposed to the chloroform vapour remained dark, while the other became gradually pale. On re-examination of the former after some hours, each web presented stripes of full diffusion of pigment alternating with others in a medium condition; their direction being at right angles to the margin of the web. The longitudinal folds in which the webs had happened to be, had prevented the chloroform vapour from gaining equally free access to all parts; yet the chromatophorous cells in the stripes that had been thus partially protected from its influence had been incapable of complete concentration, showing that even the exceedingly slight degree of action which the chloroform could have exerted upon these places sufficed to diminish, though not to destroy, the functional activity of the pigmentary tissue.

In one of the experiments performed in order to determine the effect of mechanical violence, as before alluded to, the pigment remained unchanged for days in the area which had been pinched, while varying in other parts of the web; yet, though great excess of red corpuscles existed in the vessels of the affected spot, they never ceased to move; showing that the functions of the pigment-cells might be completely suspended by a degree of irritation short of that which occasions actual stagnation of the blood.

The same thing was afterwards[1] seen in a case in which a small drop of wood-vinegar was placed upon one of the webs of a frog which had been deprived of the power of voluntarily moving the limbs by passing a knife between the occiput and the atlas, so as to sever the brain from the cord. The fluid being thus allowed to lie quite undisturbed, did not spread at all upon the web, which was dry before it was applied. It produced its effects very slowly, so that, after the lapse of three and a half hours, the blood in the area covered by it, while everywhere presenting inflammatory appearances, was still only partially

[1] This experiment was performed subsequently to the reading of the paper.

stagnant. Yet throughout this space the pigment retained exactly the same moderate degree of diffusion as it had at the beginning of the experiment, although in the interval complete concentration had taken place elsewhere ; and a very striking contrast was presented between the stellate pigment with the adhesive though still moving blood-corpuscles, where the web was wet with the vinegar, and the dotted pigment and perfectly healthy circulation in the dry parts immediately adjacent.

Seeing, then, that complete suspension of the pigmentary functions may be caused by an amount of irritation which induces only a minor degree of congestion, and further, that (as we learn from the experiment with chloroform vapour) a still milder operation of an irritant renders these functions sluggish though not completely arresting them, we seem to have sufficient evidence that impairment of the functional activity of the chromatophorous cells occurs in the very earliest stages of that primary change in the tissues which leads to inflammatory derangement of the blood.

It was seen in the ammonia experiment related above, that resolution having taken place in the congested area, the pigment-cells of the part recovered the faculty both of diffusion and concentration. This might have been pretty confidently predicted ; for as congestion is a necessary consequence of the disorder produced in the tissues by irritants, we might have been almost sure that the return of the vital fluid to that healthy condition in which it is fit for free transmission through the vessels, must be preceded by a restoration of the living solids to their normal state. In the case alluded to, however, no sign of recovery of the pigment-cells appeared till after the circulation had become re-established ; and even when several hours had elapsed, they still remained paralysed in the central part of the area on which the ammonia had acted. This is in harmony with the fact lately pointed out, that complete suspension of the pigmentary functions may accompany a state of the blood short of actual stagnation ; and both appear to depend upon the circumstance that the chromatophorous cells are an extremely delicate form of tissue.

The rate of recovery of the pigment-cells varies greatly, however, in different cases, and in this respect much depends upon the nature of the irritant. An example of an agent of this class producing only very transient effects on the pigmentary functions is presented by carbonic acid. It has been before mentioned that the immersion of a living frog for about a quarter of an hour in water highly charged with that gas, gives rise to complete stagnation of the blood in the webs, although the heart still continues beating, but that resolution occurs after the animal has been exposed for a while to the atmosphere. With a view to ascertaining whether the congestion was due to the direct action of the acid upon the tissues, I made the following experiment. Having killed a dark frog and amputated both legs, and ascertained by microscopic examination that the pigment was fully diffused in the webs, I put one limb into a bottle of 'aerated water' and the other into ordinary water: the latter soon became pale through post mortem concentration, but the former remained as dark as ever during the two hours for which it was retained in the solution of carbonic acid, the direct action of which upon the bloodless tissues was thus demonstrated. An hour after the limb had been taken out, however, it was evidently recovering, being distinctly lighter in colour than it had been, and two hours later it was quite pale, and the pigment in the webs was found to be in almost the extreme degree of concentration. In subsequent similar experiments I left the leg in the aerated water for a longer time, during which it always retained precisely the same tint that it had when first introduced; and, if left for many hours, showed signs of loss of vitality, by the early supervention of cadaveric rigidity and exfoliation of the epidermis; but if it was taken out within about four hours, the pigment-cells recovered completely; and in one case a leg not removed for nine hours regained, nevertheless, to a considerable extent, the faculty of concentration.[1] Thus it appears that carbonic acid, though exercising a powerful sedative influence upon the tissues, and paralysing for the time their vital energies, so as to give rise to intense inflammatory congestion, yet, even after a very protracted action, leaves them in a state susceptible of speedy recovery.

Here we see for the first time a satisfactory solution of the much-debated problem of the cause of congestion of the lungs in asphyxia; for there can, I conceive, be no doubt that the pulmonary tissues, exposed under ordinary circumstances to the influence of a free supply of oxygen, suffer, like those of the frog's web, from the vicinity of an abnormal proportion of carbonic acid, and inflammatory congestion is the necessary consequence. At the same time, the rapid recovery of the lungs from asphyxial congestion of considerable duration, when the normal atmosphere is readmitted, finds an equally close parallel in the speedy return both of the pigment-cells and the blood to the healthy condition when the foot of the frog is removed from the aerated water.

But the most important lesson to be learnt from these simple experiments with carbonic acid upon amputated limbs, is that the tissues possess, independently of the central organs of the nervous system, or of the circulation, or even of the presence of blood within the vessels, an intrinsic power of recovery from irritation, when it has not been carried beyond a certain point; a principle of fundamental importance, which has never before, so far as I am aware, been

[1] This observation was made subsequently to the reading of the paper.

established or conjectured. It applies equally in the case of other irritants. Thus having transmitted for about a quarter of a minute, through one of the webs of a dark amputated limb, powerful galvanic currents, such as I had before ascertained to cause stagnation of the blood when operating for an instant upon the living animal, I found, after the lapse of an hour and a quarter, that the process of concentration had advanced considerably in the next web, but in that on which the galvanism had acted had only just commenced, even in the parts most remote from the point to which the poles of the battery were applied; while in the vicinity of that spot the state of full diffusion still continued. After the lapse of three more hours, however, the pigment was almost fully concentrated in the part of the web where it was before only slightly so; and even where it had been most directly subjected to the galvanic influence, it had undergone a certain, though very slight degree of the same change, the chromatophorous cells having even there partially recovered their functions.

This inherent power in the tissues of recovering from the effects of irritation, explains the occurrence of resolution in an amputated limb, such as I once observed in a case where a moderate amount of congestion had been induced under the action of oil of turpentine before the animal was killed, and the blood resumed to a great extent its normal characters in the vessels several hours after the limb had been severed from the body.

The return of the blood along with the tissues to the state of health is a very interesting circumstance. Whether it depends upon an intrinsic power of recovery on the part of the vital fluid, or on the living solids resuming an active operation upon it, is at present uncertain; but in the meantime, the phenomena of resolution already assume a far more intelligible aspect than heretofore, on the hypothesis that the tissues generally are endowed with the same faculty of self-restoration as the pigment-cells.

It may be well to give here a list of all the agents whose effects upon the pigmentary functions I have investigated. They are as follows: Mechanical violence, the galvanic shock, desiccation of the tissues,[1] dry heat, warm water at 100° Fahr., intense cold, caustic ammonia, a strong solution of common salt, carbonic acid, acetic acid, tincture of iodine, chloroform, oil of turpentine, mustard, tincture of cantharides, and croton oil.

These are all of them irritants, i.e. give rise to inflammatory congestion through their direct action upon a vascular part, as I have witnessed in the frog's web in every case except that of cold, the influence of which in causing

[1] The effects of deficiency of moisture in the web were observed in amputated limbs, in which I have seen both suspension of pigmentary functions from this cause and recovery from that state after the application of water. While the circulation is going on in the living animal I have not found desiccation of the web to occur, unless the tissues had been weakened more or less by irritation.

intense inflammation in the human subject is, however, familiar to all.[1] All of them also afforded, in their effects upon the pigment-cells, ocular evidence of impairment of the functional activity of the tissues on which they act; and considering the number included in the list, and their great variety in essential nature, we need not hesitate to admit that similar effects are produced by the entire class of irritants.

There is another tissue in the frog's web which discharges functions apparent to the eye, viz. the arterial muscular fibre-cells, the contractions of which are readily recognized in consequence of the changes of calibre which they produce in the vessels; and the manner in which the arteries are affected in a congested part of the web indicates that the muscular, like the pigmentary tissue, has its functional activity impaired by a certain amount of irritation. Thus I have repeatedly been struck with the fact, and noted it before I knew its significance, that an artery running through a limited area on which an irritant has acted, remains dilated in the spot, although it may vary in other parts of its course. This I have observed in one experiment with mustard, in one with acetic acid, in two with ammonia, and in one with heat. In the last-mentioned case the appearance was particularly striking, from the circumstance that two arteries happened to pass through the burnt part, and were constricted to absolute closure in the rest of their course, contrasting strongly with their fully dilated state within the area.

In the ammonia experiments also the artery concerned was, in the progress of each case, seen to be completely constricted beyond the congested area, though still dilated within it. The limitation of this effect on the arteries, to the extent of the part acted on by the irritant, proves that it is the result of its direct action on the tissues; differing remarkably in this respect from the dilatation of the vessels, which is produced indirectly through the medium of the nervous system, and affects a wide space round about the spot irritated.

But with regard to both the muscular fibre-cells of the arteries and the pigment-cells, it may fairly be questioned whether the diminution of power to act resides in them or in those portions of their nerves which are situated in the irritated region. The view that the nerves are paralysed by irritants is consistent with the benumbing influence well known to be exerted upon the human skin or mucous membranes by some of those agents, e.g. mechanical violence, the galvanic shock, cold, and chloroform. I have also observed, as before

[1] The only experiment which I made with cold was performed by introducing a test-tube, containing a dark amputated limb, into a freezing mixture of ice and salt at about 20° Fahr. for ten minutes. When the frozen limb had thawed, I ascertained, on microscopic examination, that the pigment had undergone a slight degree of post mortem concentration, but five hours later it was still in much the same condition.

alluded to,[1] that mustard produces a similar result on the cutaneous sensory nerves, and hence it seems probable that the same is true of the whole class of irritants. Again, the diffusion induced by mustard, croton oil, and cantharides indicates, according to what we have seen to be its most probable explanation, that the nerves of the pigment-cells suffer impairment of functional activity under the action of these three substances. On the other hand, the fact that diffusion is arrested equally with concentration by most irritants, appears to prove that the chromatophorous cells are themselves also affected with loss of power ; for, as has been before alluded to, the withdrawal of nervous influence from them in a healthy state of the tissues invariably gives rise to diffusion, and the same result would necessarily follow the action of an irritant which merely paralysed the nerves. I have also observed, on two occasions, after the energetic operation of an irritant upon a part of a web containing a large artery,[2] that drawing the point of a needle firmly across the vessel failed to induce the slightest contraction in it, even at the very point crossed by the needle ; proving that the muscular fibre-cells had lost their irritability. At the same time it is by no means improbable that the nerves of the arteries may suffer before their muscular constituents, just as in the intestines, after death, the functions of the intrinsic nervous apparatus are lost some time before muscular contractility ceases.[3]

The question whether the suspension of function induced by irritants is confined to the nerves or affects the tissues generally, being one of great interest, I was anxious to obtain clear evidence regarding it ; and it occurred to me that valuable information would probably be derived from observing the effects of such agents upon the action of the cilia, which, though not present in the web of the frog, exist in abundance upon the mucous surfaces of the mouth and oesophagus of that animal. Dr. Sharpey, in his celebrated article 'Cilia' in the *Cyclopaedia of Anatomy and Physiology*, mentions experiments made by Purkinje and Valentin, and also by himself, with a great variety of substances, including among the rest some irritants, which, when applied with sufficient energy, arrested completely, by their chemical action as it was supposed, the

[1] See p. 234.

[2] The main arteries lying between the layers of skin of which the web consists, are not so speedily acted upon by irritants as the capillaries of the dermis. This is most marked in large frogs with thick webs. In one such specimen, a drop of chloroform caused first stagnation and then discoloration from chemical action on the blood in the capillaries of the dorsal layer of the web to which it was applied, while a main artery lying beneath still contained blood of natural appearance, and showed evidence of languid contractility, while in the capillaries of the plantar layer of the web, the circulation was still going on in a pretty healthy state. This frog, however, seemed endowed with unusual powers of vitality in the tissues. This observation, as well as that in the text to which this note refers, was made subsequently to the reading of the paper.

[3] See the paper 'On the Functions of the Visceral Nerves', before referred to (p. 87 of this volume).

movements of the lashing filaments. It is evident, however, that in order to produce effects at all comparable to the state of the tissues of the frog's web in congestion, it would be necessary to adopt some more delicate method of experimenting, and the most eligible means for this purpose seemed to be to allow an irritating vapour to play upon a ciliated surface. Accordingly, on the 30th of November, 1857,[1] having cut off a small piece of the tongue of a frog killed about an hour before, and placed it upon a slip of glass under the microscope, with just enough water to permit the free play of the cilia, I held near to it a piece of lint soaked in chloroform, keeping my eye over the microscope. The effect was instantaneous cessation of the previously rapid action of the cilia, which now stood out straight and motionless, like the hairs of a brush. I now immediately withdrew the lint, after which the same state of complete inaction continued for about half a minute, when languid movements began to show themselves, and after the lapse of five minutes more the ciliary action was going on pretty briskly in some parts, and ten minutes later seemed to have almost completely recovered.

Thus chloroform vapour produced in the ciliated epithelium-cells a condition precisely similar to that brought about in the pigment-cells by irritants applied so as to cause inflammatory congestion of the web, viz. a state of suspension or temporary deprivation of functional activity. And as the removal of the epithelium-cells from the surface on which they grow does not arrest the movements of their cilia, no mere paralysis of nerves could account for this result, which necessarily implied that the epithelial tissue itself was affected with loss of power to discharge its accustomed functions. In repetitions of this procedure upon the same and other portions of the tongue, I did not generally get complete cessation of movement of all the cilia, but usually some retained a languid action, which improved after the chloroform had been removed. In one instance, however, the same perfect stoppage took place as in the first case, and the recovery was also very general, though the returning action was languid. Under these circumstances, a piece of lint dipped in strongest liquor ammoniae was brought within about $1\frac{1}{2}$ inches of the object, and retained there for about fifty seconds, during which time the ciliary motion became progressively and greatly diminished, and within twenty-five seconds of the removal of the lint, had ceased altogether. Some water was then added, so as to get rid of the absorbed alkali, when the cilia soon began to move again, and within about three minutes their play was more vigorous and general than before the ammonia was used, and three minutes later it was universal, as it was prior to the application of the chloroform. On another occasion, in a

[1] This date indicates that the experiments on the cilia have been performed since the paper was read.

different animal, the cilia having been ascertained to be in rapid motion on a fresh piece of tongue, lint containing liquor ammoniae was held at a short distance from it for thirty-three seconds. The cilia very soon grew languid, and by the end of the time mentioned had quite ceased to act. The lint was at once withdrawn, but no recovery occurred; the operation of the irritant had been rather too energetic, and the vitality of the tissue had been destroyed. A languid state of the cilia was also produced by placing freshly prepared mustard near them, and improvement took place when it had been removed; but the essential oil itself, applied on lint like the chloroform and ammonia, though not acting so rapidly as might have been expected, permanently arrested the vibratile filaments. The vapour of strong acetic acid, if acting for four seconds, caused great diminution of the motion, and in another instance arrested it completely in five seconds. I did not, however, see any recovery from the effects of this agent, which produced obvious organic injury in the cells. The introduction of a portion of the mucous membrane of the mouth into a bottle of aerated water for about twenty minutes gave rise to permanent stoppage of the cilia, and similar treatment for three or four hours caused disorganization of the epithelium, whereas the same period of immersion in ordinary water did not arrest the cilia. Powerful interrupted galvanic currents, transmitted for a few seconds through a particular spot in a piece of tongue on which the cilia were in free movement, abraded a portion of the epithelium there, and arrested completely the cilia of adjacent cells still *in situ*, and rendered those of other parts of the specimen extremely languid in their action. But the most satisfactory results were obtained from experiments with heat, which has the great advantage over chemical irritants, that it leaves no material behind it to act upon the delicate tissue. On the 14th of December, 1857, having ascertained that steeping a piece of the tongue of a frog for five minutes in water of 110° Fahr. caused total and permanent cessation of ciliary action and desquamation of the epithelium, at 9^h 9^m p.m. I placed a portion of that organ, in which the vibratile movements were equable though rather languid, in water at 100° Fahr., and retained it there for a minute and a quarter, when it was transferred to cold water. On examining it after the lapse of nearly two minutes, I found the cilia acting decidedly more briskly than at first, but in the course of the next quarter of an hour they flagged very much, and in many parts ceased to move altogether. By this time I had fixed the specimen securely at the bottom of a glass trough, which I now suddenly filled up with water at 102° Fahr., and on first catching sight of the object, within a quarter of a minute of this procedure, found all the cilia absolutely motionless. I then at once drew off the warm water with a siphon previously arranged; and no sooner had this been done, than movements already began to show themselves in the cilia, and their action increased rapidly on my filling up the trough with cold water, and in a short time was all but universal and brisk, far superior to what it was before the hot water was put in. After a few minutes more, however, it was again very languid, and ceased entirely in many parts. I now, at $9^h\ 38^m$, filled up the trough with water at 104° Fahr. : at $9^h\ 38^m\ 17^s$ the cilia were almost all motionless ; by $9^h\ 38^m\ 55^s$ the trough had been again emptied, but at $9^h\ 39^m\ 5^s$ there was even less movement seen. Cold water was again poured in at $9^h\ 39^m\ 35^s$, and after eighteen seconds, action was reappearing in the cilia, and it continued to increase during the next seven minutes, at the end of which time it was again almost universal. At $9^h\ 52^m$ the cold water was drawn off, and the same condition of the cilia having been ascertained to exist, the trough was, at $9^h\ 52^m\ 27^s$, filled up again with water at 104° Fahr. ; eighteen seconds after this had been done, the ciliary action was found much diminished, but had not fully ceased ; and after nine seconds more, during which the warm water was drawn off, the cilia were still acting very slightly. Within twenty-three seconds of this time the trough was again filled with cold water : now, however, the epithelium was in many parts beginning to exfoliate, swelling up by endosmose in obedience to the ordinary laws of chemical affinity, and so indicating that it was losing its vitality. I also lost sight of the precise spot which I had been observing, but noticed that ciliary action was again going on pretty quickly in some places. There can be no doubt, although there was no opportunity for observing the fact, that the first immersion in hot water caused cessation of the ciliary action ; and that being admitted, we have in this case suspension of function and recovery four times repeated in the same fragment of tissue in consequence of as many applications and withdrawals of the irritant. It is a curious circumstance that each recovery, except the final one, brought up the action of the cilia for a time to a better state than they had just before the last introduction of warm water. But the discussion of this and other circumstances in this case will be best reserved till after the mention of another set of experiments.

In order to eliminate the nerves completely from among the causes both of the suspension of function produced by irritants and the recovery from that state, it seemed desirable, if possible, to observe those occurrences in detached epithelium-cells, and on the 22nd of January, 1859, I made the attempt to do so. At first, however, it proved more difficult than I had anticipated. It was of course easy to obtain the material to operate on, by gently scraping the surface of the palate of a recently killed frog with a knife, and placing the mucus-like product on a plate of glass with a drop of water. But the tissue thus separated from its connexions was in an exceedingly delicate condition, and any agent used for arresting the action of the cilia was very apt to destroy at the same time the vitality of the cells. Thus when the object was warmed by placing the glass plate on a piece of iron at about 100° Fahr. for half a minute, the vibratory movements were arrested, but never recovered, and in a short time the cells swelled up by endosmose. It appeared probable that the tissue had suffered during the time required for the cooling of the glass: and in order to avoid this, and also prevent the object-glass becoming obscured by vapour from the warm water condensing upon it, the epithelium was placed between two slips of thin covering glass, kept from too close approximation by fragments of the same material interposed, the whole forming a layer so thin that it would be rapidly heated if any hot body were placed in its vicinity, and cooled as quickly on its removal. A small cautery iron, with a bulbous extremity about as big as a hazel-nut, just too hot to bear in contact with the finger, was now put behind the stage of the microscope, within about three-quarters of an inch of the object, the diaphragm plate having been removed to afford room for this being done without interfering with the light sent up by the reflector. The result, which I watched from the first, was the same that I had once before observed from the very gentle application of heat to a portion of a frog's tongue, viz. primary increase in the action of the cilia which had previously been languid,[1] but which, within ten seconds of the approximation of the cautery, were moving with great rapidity, and continued to do so for about twenty-five seconds, at the expiration of which their motion was seen to be diminishing, and after another minute and a half it was considerably more languid than at the beginning of the experiment. The cautery being now removed was found to be much cooled though still warm, and its withdrawal did not affect the cilia, which still remained much in the same state after the lapse of eight minutes. I now repeated the experiment upon a fresh portion of epithelium, but this time used the cautery red hot, placing it about 2 inches behind the object: no sooner had this been done than the action of the cilia became excessively increased, but this did not continue for more than five seconds, when they became perfectly motionless. The hot iron was now at once withdrawn, but the cilia under special observation did not recover. In other situations in the same specimen, however, movements were observed in the course of the following minute, and it was still continuing seven minutes later, when a part having

[1] Professor Weber, of Leipsig, observed several years ago that the action of cilia upon epithelium cells removed from the human nostril was increased by gentle warmth, but retarded by cold. In that case the elevated temperature was natural to the tissue, and might be supposed to operate by restoring it to its normal conditions. In the cold-blooded reptile, however, the accelerated movement under the influence of heat has, of course, a very different significance.

been brought into the field where there were two considerable groups of cells in moderate activity, the cautery was again applied at a distance of about $2\frac{1}{2}$ inches. The motions of the cilia immediately became distinctly increased, but, as in the former case, this condition gave place in five seconds to universal quiescence. The iron was then removed, and on re-examination after three minutes, the cilia were again moving, though in a somewhat languid manner in both parts of the field. For the sake of confirmation I again operated in a similar manner upon another specimen, on which I performed no less than five successive experiments with similar results in all. In the first three of these trials I had the very same cilia under observation, and saw them time after time become first increased in action and then arrested under the influence of the cautery, and gradually recover after its removal. In some instances the times of cessation and of recovery were noted as follows :—In the first the cilia were arrested in two seconds after the application of the hot iron, but the exact time of recovery was not observed ; in the second, cessation of movement was produced in two seconds, and return began in fifteen seconds ; in the third, cessation was in fifteen seconds, and recovery also in fifteen seconds ; in the fourth, the times were not noted ; in the fifth, movement ceased in about two seconds and returned in twenty. The experiments were performed within about five minutes of each other, or something less. It is also to be remarked, that there were some slight differences in the degree of heat of the cautery and its vicinity to the object.

These experiments are as instructive as they are simple and easy of performance. They show conclusively that a component tissue of the animal frame may, independently of the nervous system, have its actions either excited or paralysed by the direct operation of an irritant upon it, and that it may possess an equally independent power of recovery. Also in the accelerated movements of the cilia elicited by very gentle heat, as compared with the cessation of their vibrations under a higher temperature, we have a striking confirmation of the view which I had taken of the relaxation of the arteries and hollow viscera in consequence of nervous irritation.[1] For the law which we thus see regulating the effects of heat upon the epithelium-cells is precisely that which I had inferred must govern the action of afferent nerves upon nerve-cells ; this law being, that an agency which, when operating mildly, stimulates a tissue to increased activity, may, when more energetic, temporarily arrest its functions. Whether or not the converse always holds, viz. that any agent which is capable of suspending the functional activity of a tissue may also excite it if applied with sufficient gentleness, or, in other words, whether irritants

[1] Vide *antea*, p. 232.

are in all cases also stimulants, seems very doubtful. As regards the nerves, such does appear to be the case; for while many, and probably all influences which induce inflammatory congestion cause temporary paralysis of sensation in parts on which they act severely enough, they all stimulate the afferent nerves in the first instance, as is shown by the reflex changes in the calibre of the arteries which occur round about any irritated spot. The nervous centres, too, present an illustration of the same principle, not only in the effects produced upon them by the nerves, as lately alluded to, but also in the excitement well known to be occasioned by small doses of many sedative narcotics, such as alcohol, opium, and chloroform, which may be regarded as special irritants of the nervous centres. In the case of the cilia, I have not observed primary increase of movement to be induced by any agent besides heat; but I am not prepared to say that it might not by careful management be made to occur with some other irritants.

The pigment-cells in the common frog give very little indication of the stimulating properties of irritants, as is evident from several of the experiments which have been recorded in this section. In the tree-frog, however, as we are informed by the German authorities, a part of the integument subjected to such influences rapidly assumes a pale tint, and that even in a portion of skin removed from the body. I have also several times noticed, after pinching the web of a common frog, that, although in the spot actually squeezed, the pigment-cells were deprived of their power of changing, a pale ring about one-sixteenth of an inch in breadth has gradually formed in its immediate vicinity in the course of the next hour; whence it seems probable that direct irritation tends to excite concentration in the English species as well as in the continental, but that in the former the effect is developed much more slowly, so that it is apt to pass unnoticed. I further, on one occasion, saw post mortem concentration greatly accelerated by heat.[1] It is doubtful, however, whether these results are due to direct action upon the pigment-cells; for in the tree-frog, as well

[1] This observation was made as follows:—On the 2nd of December, 1857, having amputated the legs of a dark frog, I put them both into water of 100° Fahr., but removed the left limb within six minutes of its immersion and placed it in cold water, leaving the right for a quarter of an hour longer, at the end of which time it was considerably paler than the left, and the microscope showed that its pigment was more concentrated. But while the warm water had accelerated the process of concentration up to a certain point, it had ultimately paralysed the pigment-cells and rendered them incapable of further change; so that the right limb remained permanently of the same colour as when removed from it, whereas in the left, which had been subjected for a much shorter time to the noxious agency, concentration continued to advance, so that in twenty-five minutes that leg was as pale as the other, and after an hour more it was a good deal the lighter of the two. I may further mention that rigor mortis was already carried to the extreme degree in the muscles of the right limb when taken out of the water, but in the left this change did not commence till about twelve hours later. At this period the pigment in the left limb still showed signs of retaining its functions, while that in the right had a dirty, indistinct appearance, indicating that it had lost its vitality.

as in the English kind, the pale tint was not confined to the precise spot operated on, but affected a limited area of surrounding tissue ; whence it seems likely that it is developed through the medium of a local nervous apparatus contained in the skin.[1] If this be true, we have no proof that the pigment-cells are capable of being stimulated except by nervous influence, although they are, as we have seen, peculiarly susceptible of suspension of function through the direct operation of irritants upon them.

With regard to the nature of the change experienced by the tissues when temporarily deprived of power by irritants, the primary increase of motion of the cilia, lapsing into quiescence, under the operation of heat, may suggest the idea of exertion followed by exhaustion. But that the state of incapacity is not dependent on previous action, seems clear from the fact that in the pigment-cells it is maintained and aggravated by an irritant continuing in operation after complete suspension of function has been induced, the same kind of effect being still produced upon the tissues which are unable to act as upon healthy parts. As an illustration of this, I may revert to the results of immersion of an amputated limb in aerated water. The carbonic acid, as we have seen, entirely prevents the occurrence of post mortem concentration, implying that the powers of the chromatophorous cells are completely suspended by it within a few minutes at most of its first acting on the part ; yet, however long the tissues thus paralysed are kept subjected to its influence, they remain without any sign of action. They will, however, recover speedily and completely if soon taken out and exposed to the air, so that the irritating gas may be dissipated ; whereas if retained for several hours in the aerated water, they may, indeed, have their powers restored to a certain extent on removal from it, but exhibit only very feeble action. Such facts as these prove conclusively that the tissues may have their functional activity impaired without loss of vitality by the direct action of irritants, independently of any stimulating effects which may be at first produced by them ; and also that the influence thus exerted is of an injurious tendency.

The imperceptible transition from suspension of function to loss of vitality displayed by the long-continued operation of carbonic acid upon the pigment-cells is also well illustrated by some of the experiments upon the cilia, especially those with heat and ammonia, which, unless employed with extreme caution, not only permanently arrested the vibratile filaments, but reduced the epithelium-cells to a condition in which they were amenable to the ordinary laws of chemical affinity. All irritants appear to be agents which, if operating with sufficient energy, completely destroy vitality, probably by inducing, through chemical

[1] See the paper ' On the Cutaneous Pigmentary System ', before referred to, p. 48.

or physical action, an irreparable derangement of the molecular constitution of the tissues. Their essential property, however, is that of causing, when applied somewhat more mildly, a minor degree of disturbance or disorder in the component textures of the body, which are rendered for the time being unfit for discharging their wonted functions,[1] though afterwards, by virtue of their innate powers, capable of spontaneous recovery, the rapidity and completeness of which bears an inverse ratio to the intensity and duration of the previous irritation. Lastly, these same noxious agents, if in a still more gentle form, operate, upon some of the tissues at least, as stimulants, rousing them to increased exertion of their vital functions. How this effect is brought about must I believe, be only matter of uncertain speculation, so long as the real nature of life in the animal frame remains, as it probably ever will remain to our finite capacities, an impenetrable mystery.

It is an interesting circumstance that, in the experiments with warm water, the cilia, after recovering from the state of quiescence, moved for a while more briskly than they did immediately before the application was made. This increased action cannot be attributed, like the primary acceleration resulting from very gentle warmth, to a mild operation of the irritant ; for the epithelium-cells must have been completely cooled down before it commenced. It must therefore be regarded as a true reaction on the part of the tissue, whether dependent on accumulation of vital energy during the period of suspended function, or excited, as by an irritant, by the state of disorder which the warm water had induced, seems uncertain.

Considering the number and variety of the functions which direct observation has shown to be suspended by irritants, viz. pigmentary concentration and diffusion, ciliary motion and nervous action, it appears probable that all the vital processes are liable to similar temporary arrest.

Different tissues, however, seem to differ in the facility with which they are affected by irritants. The pigment-cells are very susceptible to their influence as is indicated by the complete paralysis which we have seen to be produced in them by agencies that give rise to only a minor degree of inflammatory congestion ; and also by the circumstance which I have often observed in the web of the frog, that, as in the choroid coat of the human eye, they become absorbed in parts which have been injured, having been deprived of vitality by causes which inflicted on other textures only a recoverable lesion. The epithelium-cells, too, are very sensitive to irritation, exhibiting its results more rapidly than can be accounted for merely by their exposed situation. In those which

[1] The word 'irritant' is etymologically ill adapted to express the possession of this property ; but as it is universally employed in professional nomenclature, it is perhaps best to continue to use it.

invest the mucous membrane of the mouth, the cilia with which they are provided furnish the opportunity of which we have availed ourselves, of observing the stage of suspension of function in consequence of very gentle treatment; and though the epidermis does not admit of this, it shows the further stage of loss of vitality by exfoliating after an amount of injury from which the immediately subjacent tissues readily recover. John Hunter was unquestionably correct in the opinion that the elevation of the cuticle in vesication depends not only on the effusion of serum beneath it, but on a primary separation arising 'from a degree of weakness approaching to a kind of death in the connexion between the cuticle and cutis '.[1] For I find that in an amputated limb free from blood, although no effusion of serum can occur, the epidermis becomes speedily loosened in a part to which an irritant is applied, as for example, in a web treated with oil of turpentine, whereas it remains elsewhere firmly attached for days if the weather be cool.

The temporary abolition of the normal relations between the blood and the tissues in inflammatory congestion,[2] must be added to the list of instances of suspension of vital properties by irritation. The tissues the healthy state of which seems most likely to be essential to that of the vital fluid, are those contiguous to it, viz. the walls of the blood-vessels; and that these are really deprived of their vital endowments during inflammation, seems implied by the character of the material which is transmitted through them in that condition. For we have seen that the vascular parietes differ, in the state of health, from all ordinary solids in being destitute of any attraction for the fibrine, if not positively repelling it,[3] and that this is probably the cause of the merely serous character of the effusion which takes place in mechanical dropsy depending upon abnormal pressure of the blood within healthy vessels. On the other hand, the exudation of the liquor sanguinis in its integrity, such as occurs in severe inflammation, cannot, I think, be satisfactorily explained by the mere abnormal pressure of the blood produced by dilatation of the arteries and concomitant obstruction in the capillaries; but seems naturally accounted for on the hypothesis that the walls of the vessels, like other tissues, lose, for the time, in inflammation, their vital properties, and, acquiring an attraction for the fibrine like that exercised by ordinary solids, permit it to pass without opposition through their porous parietes.

It may be well to present a brief summary of the principal results arrived at in the present section.

It appears that the various physical and chemical agents which, when

[1] *Works of John Hunter*, Palmer's edition, vol. iii, p. 349.

[2] See close of last section.

[3] Vide *antea*, p. 241.

operating powerfully, extinguish the life of the constituents of the animal body, produce by a somewhat gentler action a condition bordering upon loss of vitality, but quite distinct from it, in which the tissues are, for the time being, incapacitated for discharging their wonted offices, though retaining the faculty of returning afterwards, by virtue of their own inherent powers, to their former state of activity, provided the irritation have not been too severe or protracted. This suspension of function or temporary abolition of vital energy is the primary lesion in inflammatory congestion ; the blood in the vicinity of the disabled tissues assuming the same characters as when in contact with ordinary solid matter, and thus becoming unfit for transmission through the vessels ; while the return of the living solids to their usual active state is accompanied by a restoration of the vital fluid to the healthy characters which adapt it for circulation.

CONCLUSION

It remains to glance at the application of the principles established in the preceding pages to human pathology.

The post mortem appearance which is universally admitted to indicate that the early stages of inflammation have occurred during life, is intense redness, depending essentially not upon peculiar distension of the vessels with blood, but upon abnormal accumulation of the red corpuscles in their minutest ramifications. A beautiful example of this condition, developed idiopathically, was presented by the case of incipient meningitis mentioned in the Introduction, in which the vessels of an affected spot of pia mater were filled with a crimson mass of confusedly compacted corpuscles, exactly as in an area of the frog's web to which mustard has been applied. The derangement of the vital fluid in the human subject being thus closely parallel to that which we have studied in the batrachian reptile, we can hardly doubt that in the former, as in the latter, the living solids are in a state of more or less complete suspension of functional activity during inflammatory congestion. This view is supported by the effusion of liquor sanguinis in its integrity in the more advanced stages of the disease in man, and by the speedy coagulation of fibrine upon inflamed serous surfaces, or in the interior of vessels affected with arteritis or phlebitis. For these circumstances, as has been before remarked, appear to indicate that the tissues are for the time being reduced still more towards the condition of ordinary solid matter. These arguments, derived from the appearances of the blood, are further corroborated by the immediate transition which is apt to occur from intense human inflammation to gangrene.[1]

[1] The degenerations of tissue which result from inflammation, ably delineated by Mr. Paget in his *Lectures on Surgical Pathology*, are additional evidence in the same direction.

But a comprehensive and complete account of the inflammatory process must embrace not merely the state to which the tissues are brought when the disease is fairly established, but also the causes which lead to it.

Inflammation is sometimes brought about in man in a way strictly analogous to that in which we induce it in the web of the frog's foot, viz. by the immediate operation of some noxious agent from without, as when boiling water is poured upon the skin. One peculiarity connected with such cases, as compared with those which are of idiopathic origin, is the great rapidity with which the various stages of the disorder are often developed. This, however, is the natural consequence of the direct manner in which the prejudicial influence is exerted upon the tissues ; the inflammatory phenomena supervening more speedily in proportion to the energy of the irritant. This principle is well illustrated by the effects of mechanical violence upon the human integument. A moderate degree of pressure applied continuously gives rise, during the first few hours, to nothing more than inflammatory congestion, which disappears soon after the pressure has been removed, as seen in the red mark produced upon the forehead by a tightly fitting hat. But if such treatment be continued for a considerably longer period, vesication will result, as when apparatus employed for the treatment of fractures is applied too firmly for many hours together over a bony prominence. The same effect which is thus slowly developed under a moderate degree of mechanical irritation, may, however, be induced very rapidly through the same agency in a more intense form, as is shown by the bullae which are often observed in surgical practice very soon after the infliction of a severe contusion. Here the source of irritation being no longer in operation, there is no blush of redness in the vicinity dependent upon arterial dilatation, and hence such cases are often supposed to have nothing in common with inflammation ; and I have known these vesicles mistaken for evidence of gangrene, so as to lead to unnecessary amputation. The suddenness with which inflammatory oedema arises in consequence of the bites or stings of venomous reptiles is explicable on the same principle. The poison appears to diffuse itself among the tissues so as to operate directly upon them, and when extremely virulent, kills them outright ; but when less potent, produces merely a temporary though rapid prostration of their vital energies with consequent inflammatory effusion. Again, the congestion of the lungs, which comes on so quickly in asphyxia, has been before alluded to [1] as probably the result of the sedative influence which, from experiments upon the frog, we are led to believe must be produced upon the pulmonary tissue by the abnormal amount of carbonic acid in the air-cells.

In the class of cases hitherto considered, the derangement of the part,

[1] See p. 257.

and the causes which lead to it, being both, to a considerable extent, understood, the disease may, I think, be regarded as in so far satisfactorily explained. But one important lesson taught by the results of this investigation is, that it is necessary to draw a broad line of demarcation between inflammation produced by direct irritation, and that which is developed indirectly through the medium of the nervous system, whether in the immediate vicinity of a source of irritation, as around a tight stitch in the skin, or a thorn in the finger, or at a distance from the disturbing cause, as when the kidneys are affected in consequence of the passing of a bougie, or the lungs through exposure of the feet to cold. Nothing can better illustrate the importance of this distinction, than what takes place in a recent wound. In consequence of the injury inflicted by the knife, together with the subsequent manipulation and exposure, the tissues, in a thin layer at the cut surface, are thrown into that condition which leads to effusion of liquor sanguinis, the fibrine of which, speedily coagulating, remains to constitute the bond of primary union, while the serum trickling away between the lips of the wound produces the discharge which soaks the dressing during the first twenty-four hours. But neither during the exudation of the lymph in such a case, nor during its subsequent organization, is there necessarily any inflammation induced in the lips of the wound through the nervous system ; and if this complication does occur, it interferes with the healing process in a degree proportioned to its intensity. In other words, while a certain amount of inflammation as caused by direct irritation is essential to primary union, any degree of it as induced indirectly is both unnecessary and injurious.

The question how inflammation is developed through the medium of the nervous system, possesses a high degree of interest, in consequence of its bearing upon the manner in which counter-irritation operates therapeutically. In the integument, where we have the opportunity of seeing the affected part, the first indication of the supervention of inflammatory disorder around a centre of irritation is a blush of redness, which, as before shown,[1] consists, in the first instance, of mere dilatation of the arteries with rapid flow of blood through the capillaries. It is quite conceivable that arterial dilatation, carried to an extreme degree along with powerful action of the heart,[2] may so increase the tension upon the tissues as to impair their powers gradually by mechanical irritation, just as the frontal integument is affected by long-continued gentle pressure from without, as above alluded to ; for we know that when inflammation does exist, mere increase of tension upon the blood in the vessels will greatly aggravate

[1] See p. 231.

[2] It is to be observed, that in the frog, when full dilatation of the arteries lasts for days together without the production of inflammatory congestion, the state of the vessels has been brought about by a very serious operation which greatly weakens the action of the heart.

the disorder, as when an inflamed foot is kept in a dependent posture. Supposing this to be the whole mechanism of the disease, its origin would be sufficiently intelligible ; for we have seen that vascular dilatation caused by irritation operating through the medium of the nervous system appears to depend on a depressing influence produced by excessive action of the afferent nerves upon the ganglia which preside over the arterial contractions. There are, however, some circumstances, such as the dryness of the nostril which may exist in the early stages of coryza, and sudden suppression of urine in consequence of urethral irritation in cases where renal congestion becomes ultimately established, which seem to indicate that other functions as well as arterial contraction may be primarily arrested by nervous agency in the early stages of inflammation. The study of the pigmentary system of the frog has afforded proof that other tissues besides muscular fibre are under the control of the nerves, and it seems not unlikely that gland-cells or other forms of tissue may, like nerve-cells, be reduced to a state of inactivity by excessive nervous action ; and thus we seem to have a clue to comprehending what at first appears anomalous, that prostration of the vital energies of the part actually inflamed may be brought about by unusually great activity in the parts of the nervous system specially concerned with it. This, however, is a wide subject, which requires further investigation. But in the mean time we may, I think, consider as satisfactorily established the fundamental principle, that whenever inflammatory congestion, or, in other words, that disturbance of the circulation which is truly characteristic of inflammation, exists in any degree, the tissues of the affected part have experienced to a proportionate extent a temporary impairment of functional activity or vital energy.

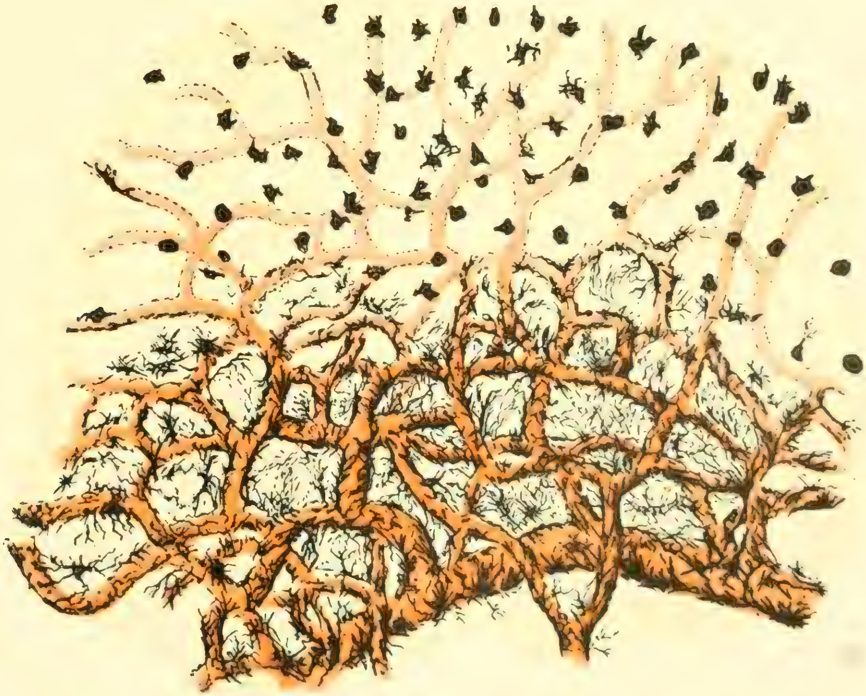
PLATE V

represents the effects produced by irritants upon the pigmentary tissue and the blood-vessels of the frog's foot.

Fig. 1 shows the results of the application of mustard to the web. The pigment was at first in the stellate condition as on the left-hand side of the sketch, and it remained permanently in that state in the part on which the mustard lay, while at the same time intense inflammatory congestion was produced there, indicated by the deep red colour of the vessels. Just beyond the edge of the mustard the irritating vapour of the volatile oil gave rise to full diffusion of the pigment (an effect peculiar to mustard and a few other irritants when acting mildly), but without material inflammatory disorder of the blood ; as seen in the stripe down the middle of the drawing. During the progress of the case the animal changed to a pale colour in the body generally, assuming the dotted aspect depicted on the right-hand side of the sketch in all parts which had not been acted on by the mustard, and thus deprived for the time being of the power of concentration. It will be observed that the blood-vessels of the healthy part are not materially smaller than those of the congested region ; the deep colour of the latter being due to their containing closely packed red corpuscles, while the former are pale in consequence of the blood within them having the normal proportion of colourless liquor sanguinis.

Fig. 2 illustrates the effects of mechanical violence. The lower half of the sketch represents parts of an area in one of the webs of a dark frog, which was pinched with a pair of padded forceps so as to give rise to inflammatory congestion. The animal afterwards grew much paler, so that in healthy parts the pigment assumed the angular or slightly stellate appearance shown in the upper part of the drawing. But on the particular spot on which the mechanical violence had operated, the chromatophorous cells being incapable of discharging their usual functions, the pigment remained in the fully diffused state in which it was at the commencement of the experiment.

Plate V



A CONTRIBUTION TO THE GERM THEORY OF PUTREFACTION AND OTHER FERMENTATIVE CHANGES, AND TO THE NATURAL HISTORY OF TORULAE AND BACTERIA [1]

[*Transactions of the Royal Society of Edinburgh*, vol. xxvii, 1875.]

PART I

ALTHOUGH the subject of the following communication has of late years attracted a great deal of attention among the public generally, it may, nevertheless, be well for me to preface my statements by a few elementary remarks.

It is well known that organic substances, when left exposed under ordinary circumstances, undergo alterations in their qualities. For example, an infusion of malt experiences the alcoholic fermentation ; a basin of paste prepared from wheaten flour becomes mouldy ; or, again, a piece of meat putrefies when so treated. The microscope shows that each of these changes is attended by the development of minute organisms. In the fermenting sweet-wort the yeast which falls to the bottom of the containing vessel is found to consist of budding cells, constituting the yeast plant, *Torula Cerevisiae,* represented in Plate VI, Fig. 2.[2] In the mouldy paste the blue crust which is the most frequent appearance, owes its colour to the spores of a species of filamentous fungus, *Penicillium Glaucum,* the commonest of all moulds, of which Fig. 1 in Plate VI represents a pencil of fructifying threads ; and the putrid flesh will be probably found teeming with bodies which, in the most typical form, consist of two little rods, connected endways as by a joint, such as are seen at *a*, Fig 3, Plate VI, characterized by astonishing powers of locomotion, and, from their rod-like form, termed *Bacteria.*

The Germ Theory supposes that the organisms are the causes of the changes ; that the germs of these minute living things, diffusible in proportion to their

[1] This communication was originally made orally to the Royal Society on the 7th of April, 1873. In preparing it for the press I have introduced various details which I was unable to enter upon at the time. I have also added facts ascertained at subsequent periods ; but the dates of the observations being always mentioned, there will be no difficulty in distinguishing between those made before and after the delivery of the original address.

[2] In the present state of uncertainty regarding the true affinities of the yeast plant, it seems justifiable to retain for it the old name *Torula Cerevisiae*, a practice which has the advantage of enabling us to apply to similar budding cells the generic name Torula, and the adjective toruloid.

minuteness, are omnipresent in the world around us, and are sure to gain access to any exposed organic substance ; and, having thus reached it, dev lop if it prove a favourable *nidus*, and by their growth determine the chemical changes ; and further, that these organisms, minute though they appear to us, form no exception to the general law of living beings, that they originate from similar beings by parentage.

Of those who oppose this theory, some attribute the changes to the oxygen of the air ; others, while convinced of the insufficiency of the oxygen theory, hold the doctrine of so-called chemical ferments, and ascribe the alterations we are considering to organic principles destitute of vitality, the organisms being regarded as accidental accompaniments ; while others, admitting perhaps the fermentative agency of the organisms, believe that they do not necessarily spring from parents like themselves, but may arise, *de novo*, from the inorganic world by spontaneous generation.

The philosophical investigations of Pasteur long since made me a convert to the Germ Theory, and it was on the basis of that theory that I founded the antiseptic treatment of wounds in surgery. The results of the treatment pursued constantly on this guiding principle have convinced me more and more of the truth of the theory upon which it was based ; and if I were to put together the facts which I have had presented to me in surgical practice, proceeding on the antiseptic system, I should be able to present an array of evidence in favour of the Germ Theory as good and convincing as experiments performed in a laboratory.

But whilst I was thus for my own part thoroughly convinced of the truth of the Germ Theory of fermentative changes, I was led about a year and a half ago to direct my attention again to the subject by a remarkable paper by Dr. Burdon Sanderson, which appeared as an appendage to a report by the Medical Officer of the Privy Council.[1] Dr. Burdon Sanderson produced evidence, of which the following may be taken as a specimen :—If a vessel like a miniature ale-glass was heated considerably above the boiling point of water, to destroy any organisms adhering to it, and, when cooled sufficiently, was charged with boiling Pasteur's solution—a fluid ingeniously devised by that eminent chemist to provide suitable pabulum for organisms, consisting of a solution of cane-sugar, some ammoniacal salt, and earthy materials derived from the ashes of yeast—the liquid being left freely exposed to the air, fungi developed in it, but no bacteria. If, on the other hand, a drop of water, say water from the tap, was introduced into the Pasteur's solution, within a few days the originally transparent liquid was rendered milky by the presence of abounding bacteria.

[1] This paper will also be found in the *Quarterly Journal of Microscopical Science*, vol. xi. 1871.

Another very remarkable fact is mentioned by Dr. Burdon Sanderson in the paper referred to. These bacteria, which have been commonly regarded as tough-lived organisms, difficult to kill, were found by him to be deprived of vitality altogether by simply drying them thoroughly at a temperature no higher than that of an incubator for the hatching of eggs, about 100° Fahr.

By this second fact he explained the first. If bacteria are deprived of all vitality by dryness, then it seemed comprehensible that the dust of the air should contain no living bacteria, and, therefore, that none should have grown in the Pasteur's solution exposed to the atmosphere in the experiment first mentioned.

Further, Dr. Sanderson was led to conclude that bacteria were the sole causes of putrefaction ; that fungi could only cause mustiness, or a comparatively insignificant alteration in organic substances.

Now, if these conclusions were strictly correct, they would affect my surgical practice in a most important manner. If it were true that the air does not contain the causes of putrefaction, then it would not be necessary for me, in carrying out the antiseptic system of treatment, to provide an antiseptic atmosphere. All that would be needful would be to purify the surface of the skin of the part to be operated upon by means of some efficient antiseptic, to have my own hands, and those of my assistants, and also the instruments, similarly purified ; and then the operation might be performed without the antiseptic spray which we now use, and no one would rejoice more than myself to be able to dispense with it.

At the same time, striking as Dr. Sanderson's facts were, I could not believe the truth to be exactly as he stated—that 'no amount of exposure has any effect in determining the evolution of microzymes' (bacteria).[1] Various considerations, including circumstances that I had witnessed in surgical practice, made me fear the news was too good to be true. I determined, therefore, to put the matter to the test by a very simple experiment.

The fluid which I used was urine, which has so often been made the subject of experiments by Pasteur and others ; but instead of employing boiled urine for the purpose, I thought that in all probability the fluid might be obtained unboiled, yet uncontaminated, by a very simple procedure. According to a principle which I enunciated about two years ago before the Royal Medical Society here, and of which I must not now give any more evidence than the fact that will immediately follow—the healthy living tissues are capable of preventing the development of these low organisms in their immediate vicinity. If that were true, although undoubtedly the skin in the neighbourhood of the

[1] See *Microscopical Journal*, vol. xi, p. 338.

meatus urinarius must contain such organisms, yet supposing the urethra to be in a state of perfect health, the tissue of the lining membrane should prevent the entrance of those organisms, even for the thousandth part of an inch, within the mucous canal. The urethra, of course, contains putrescible materials, whether it be residual urine or the mucus secreted by the lining membrane; and the intervals between acts of micturition would afford time for the organisms to spread extensively inwards if it were a tube of indifferent matter; but I hoped, in accordance with the principle which I had had reason on other grounds to believe in, that the organisms would prove unable to develop in this putrescible material, however favourable a *nidus* for their growth. If this were really the case, instead of having the urine drawn off with a catheter, with special precautions, as was done by a surgeon at Pasteur's request, if the skin round the orifice of the urethra were treated with an efficient antiseptic, say with a solution of carbolic acid in forty parts of water, the urine might then be passed from the patient from whom it should be obtained, perfectly uncontaminated, though unboiled, free from any living organisms. Accordingly, on the 10th of November, 1871, I performed the following experiment:—Six wine-glasses were heated far above the temperature of boiling water by means of a spirit-lamp. I may here remark that in the rest of this communication, wherever I use the word 'heated' (in quotation marks), I shall wish to be understood as meaning that the thing spoken of is not hot when used, but that it has been heated far above the boiling point of water, and then allowed to cool. Six glasses, then, were thus prepared, 'heated' by means of a spirit-lamp. A glass plate large enough to cover them all, and overlap them considerably, was also similarly 'heated'. Urine was then passed into these six glasses with the antiseptic precaution that I have mentioned. Two of the glasses, before being covered, received each a minim of water from the tap; and into a third a much smaller quantity of water was introduced. To the rest no water was added, but one was left exposed for twenty-four hours to the air of my study, while the other two were put at once under the cover of the glass plate. After the lapse of forty-eight hours, quite in accordance with Dr. Sanderson's statement, the two to which the drops of water had been added were turbid from the development of large and active bacteria; and the one which received a very minute quantity of water was similarly affected, though in a less degree, while the other glasses showed no change. But when twelve more hours had passed, the glass which had been exposed to the air, without the addition of any water, presented spots of opacity in the cloud of deposited 'mucus', and on examining a portion of the cloud with the microscope, I found in the first field several bacteria in full activity. But the other two which had been covered by the glass plate from the first were perfectly clear. I should say that after twenty-four hours these glasses, instead of being covered with the glass plate, were put under a glass shade common to them all ; an exceedingly rude method of experimenting, merely intended to obtain rough evidence of whether exposure to the air would or would not lead to the development of bacteria. Considering, therefore, how imperfect were the means of excluding dust, I was not at all surprised to find, in the course of a few days, that the two glasses which had remained clear longer than the rest also exhibited organisms of different kinds, into the details of which I need not enter further than to say that those of one of the glasses included distinct bacteria.

This experiment, rude as it was, showed clearly that exposure to the air might lead to the development of bacteria, provided always that the urine was free from contamination to begin with. And, further, the comparative slowness of any change in the two glasses which were neither treated with water nor intentionally exposed to dust, led me to think that in all probability, if the experiment had been performed more rigorously, I should have had no development at all in them ; or, in other words, that the method of obtaining uncontaminated urine was really trustworthy. If so, the fact was not only valuable as affording a ready means of performing experiments on the question at issue, but also exceedingly interesting in itself, as a strong corroboration of the view that the healthy living tissues prevent the development of these organisms.

Accordingly, it seemed worth while to perform another similar experiment somewhat more rigorously, and this was done on the 21st of November of the same year. Wine-glasses were ' heated ' as before, but each was provided with a separate cover, which was also ' heated '. Two of these covers were inverted porcelain evaporating dishes, which had the advantage of preventing the direct effect of lateral currents of air ; but as I had only two such dishes at hand, I used for the rest of the glasses square pieces of glass plate overlapping well in all directions ; and a glass shade was put over all as an additional protection from dust. Further, instead of having the urine passed directly into the several glasses in succession, which was an inconvenient procedure, I had it introduced, in the first instance, into a flask provided with a porcelain cap, the flask having been heated over a red fire and allowed to cool under protection of the cap, which had also been thoroughly heated. The glasses were then successively charged from the flask with as little exposure as possible. The residual urine in the flask was boiled for nine minutes, and two additional ' heated ' and covered glasses were charged with the boiled urine, and to one of these a drop of tap water was added. I shall speak of those again by and by. As regards those charged with the unboiled urine, one was exposed for forty minutes to the air of the room; one was exposed for nine and a half hours; and the other two (those with the porcelain covers), were, in the first instance, not exposed at all. The one exposed for nine and a-half hours to the air, showed, in four days, besides some minute plants of filamentous fungi, opaque spots in the cloud of mucous deposit, and next day the liquid was turbid with perfectly characteristic and abundant bacteria, and had acquired a rank, strong odour. The urine exposed for forty minutes showed indeed no bacteria, nor any torulae or other organisms except three plants of filamentous fungi, which appeared to be of three different species, judging from their differences in density and rate of growth. They continued to grow until at last they almost filled the wine-glass, the fluid above them retaining its transparency unimpaired. When they had grown too large for their wine-glass, I transferred them to a large goblet into which urine had been passed, with the same sort of antiseptic precautions as were before described, after the goblet had been heated along with its saucer-like cover, and allowed to cool under a glass shade, packed round its base with cotton-wool to exclude dust. In this goblet the fungi continued to develop; and one growing more rapidly than the rest at length overlapped and smothered them, and then continued to grow alone till, by the end of January, ten weeks after the commencement of the experiment, the goblet was almost full of the delicate white filamentous mass, which, with the bright unaltered amber-coloured liquid above, presented a very beautiful appearance. At length, in the early part of February, I observed that the whole urine had become turbid, and at the same time the fungus, which before had continued to grow steadily upwards, had suddenly collapsed into about a third of its former volume. On examination I found that the liquid had a strong smell, and contained multitudes of minute granules grouped irregularly in a different manner from that which prevails among bacteria. In bacteria, where more than two constituent elements are connected together, they are commonly arranged in a linear series, constituting what are termed leptothrix filaments, as seen in Plate VI, Fig. 3 *b* and Fig. 4. But in the case of these granules, when three or four were associated, they never showed themselves in a line, and when only two were together the members of the pair were often dissimilar in size. Yet, though unlike bacteria, there could be little doubt that these granules were some species of organism, and the natural interpretation was that it had found its way into the glass, and, developing in the urine, had rendered it poisonous for the fungus, just as is commonly seen when bacteria grow along with *Penicillium Glaucum* in urine. The bacteria occasion putrefaction in the fluid, and when this has advanced to a certain degree the growth of the penicillium is arrested.

I had before met with granules of similar size and grouping. They occurred in one of the two glasses of boiled urine in this experiment. To one of those glasses, it may be remembered, a drop of tap water was added, while the other was simply covered with a glass plate. In the former glass bacteria of usual appearance showed themselves, as was to be expected ; but it was five days before they occurred, whereas a specimen of the same urine unboiled presented bacteria in abundance in two days when similarly treated. This, I may remark, implied that the unboiled urine was a much more favourable *nidus* for the development of these organisms than the boiled liquid, and therefore a more sensitive medium to experiment with. The other glass of boiled urine, to which no water was added, continued unchanged for three weeks, which was more than could have been expected, as it was covered merely with a plate of glass, there being no room for it under the glass shade. But at the end of that time the urine became turbid, and I found under the microscope multitudes of granules, of which samples are represented at *a* in Plate VI, Fig. 5, resembling what I have described as occurring in the goblet. Plate VI, Fig. 5 *b*, represents another specimen of similar bodies which occurred in a glass of unboiled urine about the same period. I have introduced this sketch because it shows the peculiar irregular groups formed when several are together, as well as the variety of size of the individual granules.

That these granules were really organisms I had once an unexpected opportunity of proving. On the 5th of February, of the same year, I was examining some of them which had grown in a glass of unboiled urine, diluted with twice its bulk of distilled water which had been boiled and allowed to cool, and as I proceeded to sketch the group represented at c_1 in Plate VI, Fig. 5, I saw that it grew under my eyes. When I began the sketch, the lower three members of the group were a pair. About ten minutes later, at 9.4 a.m., the three had become four, as seen at c_2, where also the constituents of the other group of four are seen to have increased in bulk. By 9.30 the lower four had grown to seven, as is shown at c_3,[1] where also the left-hand granule is seen to be greatly swollen. At 9.50 the upper four granules were observed to be each faintly marked by a transverse line, and finally by 10.36 those four had become developed into eight, as shown at c_4, while the large granule most to the left was marked by a cross, indicating that it was undergoing division into four. The 'fissiparous generation' thus observed to take place was clear proof that these little bodies were really organisms ; while the manner in which the divisions occurred appeared to mark the species off from bacteria, in which the only recognised segmentation is in a line transverse to the longitudinal axis, as is

[1] There were, no doubt, in reality eight ; one of them being obscured by lying beneath the quadruple granule just formed out of one of the single ones.

illustrated by the sketches given in Fig. 4 (see explanation of the Plates). This mode of growth explained also the peculiar arrangement of the granules, which serves to distinguish it from bacteria, viz. that when three or four are present in a group they are not, as a rule, arranged in a straight line. I suggest provisionally the name Granuligera for this little organism, of which there may, for aught I know, be various species. Its distinction from bacteria is a matter of considerable interest, because, although destitute of anything like vital movement, it often renders fluids as turbid as bacteria, and like them produces a rank smell in urine, followed in a few days by strong ammoniacal odour. So far as urine is concerned, therefore, it seems to be an instance of an organism different from bacteria giving rise to putrefaction.

About this time my study suffered from an epidemic of granuligera. I could not now perform the same experiments with the same success as in the first instance: any that I tried was sure to be followed by the development of this pervading organism. I eluded it, however, by continuing the investigation in a room at the top of the house, which had been for a considerable time unoccupied. Here the results of experiments corresponded with those originally obtained in the study.

But I have not yet spoken of the two glasses of the second experiment which were not exposed, but were kept covered with the evaporating dishes under a glass shade. The liquid in both these glasses having remained unaltered for nearly a fortnight (thirteen days), I exposed one of them to the air for nine hours in my study, which is a warm room (over the kitchen), the weather being dry and frosty, and then replaced it, covered as before, under the glass shade, having previously ascertained that the odour was that of perfectly fresh urine. Two days later the cloud of mucus presented a multitude of vertical white streaks, and the side of the glass was also similarly marked, and when another day had passed the whole liquid was manifestly turbid, and there were also two little patches of scum upon the surface. On microscopic examination I found that the scum was composed of a species of torula, and that the turbidity was due to a small organism which, while motionless like granuligera, resembled bacteria in its mode of segmentation and arrangement. It is represented in the sketches given at *c* in Plate VI, Fig. 3, where it will be observed that when three elements exist together they are in a straight line, and that some of those which are in pairs present a transverse line of incipient division through each constituent portion. Occasionally this organism was met with in the form of long chains (leptothrix), and it is plainly referable to the bacteric group. But no filamentous fungus occurred from first to last in this glass, which, in that respect, was the exact converse of the one which was exposed to the atmosphere in the first instance for forty minutes, and in which, it will be remembered, filamentous fungi occurred without either torulae or bacteria—the obvious explanation of the difference being that different organisms happened to prevail in the air of the room at the two periods of exposure.

The other glass was left permanently covered; and the urine in it remained permanently free from organic development or putrefactive alteration. After the lapse of many weeks, when its bulk had been considerably reduced by evaporation, it became turbid, leading me to suspect bacteria. But on applying the microscope I found the appearance was occasioned merely by saline deposit, and the contents finally dried up into a solid residue, without undergoing any other perceptible change.

I need hardly point out how entirely such a fact as this disposes of the oxygen theory as regards this particular fluid at ordinary temperatures. Neither cover nor shade fitted closely, so that a constant interchange was taking place by diffusion between the air in the wine-glass and the oxygen and other gases of the external atmosphere; yet no putrefaction or other fermentative change occurred. Nor is the fact less significant in its bearing upon the theories of chemical ferments and spontaneous generation. The vesical mucus has been commonly regarded as the special chemical ferment of urine: but it was here present, unaltered by boiling or any other treatment, yet failing for weeks together to produce any fermentative change. And the mere fact that the liquid was received into a vessel which had been heated so as to destroy all life within it, and afterwards protected from the access of dust, ensured the absence from first to last of all organic development. It is, therefore, certain that this urine contained no materials or principles capable at ordinary temperatures of evolution into living beings.

At the same time the behaviour of the glasses which were exposed to the air in this experiment indicates that the foreign element which gives rise to bacteria, like that which occasions the growth of filamentous fungi and torulae, may enter in the form of atmospheric dust.[1]

But the results of this simple experiment were valuable in other respects. In the first place, it afforded ample proof that urine may be obtained perfectly

[1] It may be urged that the particles of dust which give rise alike to the development of organisms and to fermentative changes in a fluid like urine are not necessarily organisms, but may possibly be little bits of so-called chemical ferments which occasion chemical alterations, that in their turn lead to the evolution of organisms by spontaneous generation. Such a view, plausible as it may appear, will be shown in the sequel to be utterly destitute of scientific basis. Meanwhile we must be content with the sure step mentioned in the text, viz. the fact that neither fresh healthy urine nor its mucus contains any such evolutionary particles. I feel justified in stating this as a general truth regarding urine, since it has been found to hold not only in numerous other experiments with this liquid derived from the same source, but also when it was obtained by the same method from two other individuals.

free from organisms by merely applying an efficient antiseptic as a preliminary measure to the *meatus urinarius* ; and I have before referred to the high interest which attaches to this point.

Secondly, it showed that if an organic liquid is obtained in an uncontaminated state to begin with in a 'heated' wine-glass, covered with a 'heated' cap shaped like an evaporating dish, and further protected by a glass shade, we are secure against the introduction of any organism from without, so long as the arrangement is left undisturbed.

Further, the permanent freedom from contamination in this glass was particularly satisfactory, because, seven days after it was charged, I had removed a drachm of the liquid from it by means of a 'heated' pipette, in order to ascertain the effect of water upon the unboiled urine as above alluded to (see p. 278). If no organic development resulted from the sudden entrance of so considerable a volume of air as then passed into the glass to take the place of the liquid withdrawn, it follows that, various as are the organisms which float in the atmosphere, they constitute but a very small proportion of the abounding particles of dust which a beam of sunlight reveals in an occupied apartment.

A similar inference must be drawn from the circumstance before mentioned, that the sole result of forty minutes' exposure of one of the glasses of this experiment to the air was the development of three plants of filamentous fungi, whereas the particles of dust which fell into it during that time must have been very much more numerous.

If, then, the withdrawal of a drachm of liquid, or exposure for more than half an hour had so little effect, it was plain that the removal of one or two minims, executed nimbly so as to involve little more than momentary exposure, must be practically free from the risk of accidental contamination.

I thus became possessed of a means of making observations upon these minute but highly important organisms, which promised to yield results of a more definite character than any which had been hitherto obtained.

Various detailed accounts have been given of late years, not only of the spontaneous generation of animal and vegetable forms of more or less complexity, such as large ciliated infusoria from an infusion of hay, or torulae and penicillia from milk globules, but also of the transition of one form of organism into another. But in the latter class, as in the former, the liability to deception is so extremely great, in consequence of microscopic organisms accidentally present developing side by side with the minute objects investigated, and presenting the appearance of growing out of them, that, without the slightest doubt being thrown upon the good faith of the observers, the so-called facts are justly received with the gravest suspicion. But with the means now at our disposal the grand source of error in former similar inquiries might be eliminated, and results of a more satisfactory character might therefore be anticipated. I was thus led to prosecute the investigation far beyond what I had at first intended, and will now proceed to give a selection from the results.

That which I will mention first has reference to the origin both of torulae and of bacteria.

On the evening of the 13th of December, 1871, during a drizzling rain which had been falling all afternoon, I took a 'heated' wine-glass with its cover out into the street, and, raising the cover, allowed a few drops of rain to fall into the glass, and having covered it again and brought it back into the house, I charged it with unboiled urine from a 'heated' flask, the arrangements for obtaining the liquid being the same that have been before described. In the course of two days I noticed a tiny opaque streak proceeding vertically downwards from a point on the inside of the glass; and on the following day the streak had increased, and the cloud of mucus was speckled with numerous white points. On the fourth day, while the speckling of the cloud had increased, and the streak had become coarsely granular, two little plants of filamentous fungi were also seen floating in the clear liquid. By the fifth day the specks in the mucous deposit had assumed the appearance of coarse grains of white sand, and similar granules were sprinkled over the lower part of the inside of the glass. I removed one of these granules with 'heated' pipette, and examined it microscopically. It proved to be a very beautiful torula, composed of pullulating oval cells of great delicacy, disposed in groups, of which one is represented in Plate VI, Fig. 6 *a*. Though not very different in size from the yeast plant, it proved itself to be a totally distinct species, not only by the more delicate and less granular character of the cells, but by the fact that it grew thus luxuriantly in non-saccharine urine, in which the *Torula Cerevisiae* will only grow with extreme difficulty. For the sake of distinction I may term it *Torula Ovalis*, on account of the oval form of its cells. When ten days had elapsed after the mingling of the rain water with the urine, the white granular deposit had greatly increased, and some scum was also present on the surface, which the microscope showed to consist of the same oval torula. But the two plants of filamentous fungi had subsided and had apparently ceased to grow; the liquid, though still brilliantly clear and but very slightly affected in odour, having doubtless become unfit for their development through chemical changes induced by the torula. Another small fungus plant, observed several days before upon the side of the glass below the level of the liquid, seemed, however, to be still increasing. At this time having occasion to go into England for a few days, and being desirous of continuing the investigation, I took some of the liquid with me, decanting a drachm of it with 'heated' pipette into a 'heated' test-tube about five inches long, which I covered with an inverted test-tube of about the same length (of course also 'heated'), and packed the tube vertically in a box with cotton-wool. Five days later (on the 28th of December), having prepared some Pasteur's solution in a manner which I hoped would ensure absence of living organisms at the outset,[1] I inoculated about an ounce with half a minim of the urine in the test-tube, including some of the white deposit at the bottom. The glass, which was of course 'heated', as well as its porcelain cap, was placed under a glass shade in a room varying in temperature from about 60° to 70° Fahr. It is necessary to state, that before raising the inverted test-tube which covered that containing the urine, I carefully wiped the mouth of the former with a rag dipped in a strong watery solution of carbolic acid; without this precaution there would have been a risk of contamination of the urine-tube with some portion of cotton or dust adhering to the covering tube.[2] The urine still continued quite bright, and on examining with the microscope the residue in the pipette after the inoculation, I found it to consist of the oval torula unmixed with anything else.

Thirty-six hours after the inoculation I found the inside of the glass that contained the Pasteur's solution sprinkled over from top to bottom with a fine granular deposit resembling white sand under a pocket-lens, and about a third of the surface of the liquid was occupied by a dense white scum which microscopic examination on the following day showed to consist of oval torula cells,

[1] In preparing the liquid I deviated to some extent from Pasteur's formula, which is 100 parts distilled water, 10 parts pure sugar-candy, 1 part tartrate of ammonia, and the ashes of 1 part of yeast. I employed lump-sugar instead of sugar-candy, and reduced its proportion by one half, as it seemed to me likely to prove somewhat too strong to suit some organisms. Further, as I had not at hand a reference to enable me to ascertain how much of the mineral salts Pasteur employed, I used what seemed to me about a suitable amount for a fungus to consume, judging from the quantity that I got by incinerating a certain weight of yeast; and this, as I afterwards found, was a little more than Pasteur's proportion. My solution, then, had the following composition:—

Distilled Water	5000 grs.
Lump-Sugar	250 grs.
Crystallized Tartrate of Ammonia .	50 grs.
Dry Ash of Yeast	5 grs.

making rather more than half a pint. The liquid was introduced through a 'heated' funnel into a 'heated' Florence flask provided with a 'heated' glass cap, and was boiled and allowed to cool in the pure and covered vessel. A better method of procedure will be described in a later part of this communication.

[2] The efficacy of a strong watery solution of carbolic acid for the destruction of minute organisms was familiar to me from experience in antiseptic surgery; and it is also well illustrated by the method of obtaining uncontaminated unboiled urine described in the text. The fact is of great value in experiments on this subject, as it affords a simple and sure mode of purifying portions of apparatus which it would be inconvenient or impossible to subject to heat. And the extensive experience which this investigation has involved, enables me to state with confidence that wiping a piece of glass with a rag moistened with a solution of carbolic acid in twenty parts of water as efficiently destroys adhering organisms as heating to redness in a flame.

closely resembling those in the urine of inoculation. A group of these from the Pasteur's solution is represented at *a*, Plate VII. On the 3rd of January, 1872, I inoculated a second 'heated' and covered glass of the same stock of Pasteur's solution by introducing into it a drop from the former glass of the same fluid containing the growing organism, and in the course of the next twenty-four hours the cells of *Torula Ovalis* were again seen under the microscope in a deposit on the side of the glass. Next day, being about to return to Edinburgh, I introduced some of the contents of this second glass of Pasteur's solution into a 'heated' test-tube provided with an inverted test-tube cover, and packed the tube with cotton-wool in a box along with that containing the urine. Meanwhile, although eleven days had elapsed since the urine was decanted into the test-tube for the journey south, the liquid remained perfectly transparent, and showed no appearance of any other organism besides the *Torula Ovalis*; so that it may be assumed that the plants of filamentous fungi present in the original urine-glass had been avoided in the process of decanting, and that the *Torula Ovalis* existed in the test-tube unmixed with any other organism.

Being occupied with other matters, I did not look at these test-tubes again until seven months had passed, during which time they had remained undisturbed in the cotton-wool in which they were packed. This proved to have been a very fortunate arrangement, the long narrow form of the vessels and their covers, and the mass of cotton about them, having so interfered with evaporation, that a considerable proportion of the liquid remained in the glasses. On closely inspecting them on the 6th of August, 1872, I saw that in both the part of the glass that had been left dry by the slow evaporation was studded over with little round whitish gelatinous-looking bodies, smaller than pins' heads, which I thought might perhaps be a fungus related to the torula, a surmise which was at once verified by examination of the glass containing the urine. Having raised the test-tube cover, after wiping its lower part with 1 to 20 watery solution of carbolic acid, I succeeded in picking up with a mounted needle (passed through the flame after washing the wooden handle with carbolic solution), a portion of one of the little gelatinous bodies, and submitted it to the microscope. It proved to be made up of plants of an exquisitely delicate filamentous fungus, of which *b*, in Plate VI, Fig. 6, represents one young plant entire, giving off a branch, and *c* a somewhat larger plant, bearing two oval bodies considerably thicker than the thread from which they spring, which must be looked upon as spores (conidia). In *d*, *e*, and *f* are given portions of other filaments bearing similar conidia. Such conidia were also seen free and pullulating, either in pairs, as in *g*, *h*, and *i*, or more rarely in somewhat larger groups as at *k*, which, in fact, constituted a torula undistinguishable from the original *Torula Ovalis*.

But while some of the buds proceeding from the filaments had thus the character of toruloid conidia, differing from ordinary branches not only by their form but by their thicker and more substantial character, it was more common to see sprouts presenting the opposite condition of extreme slenderness, as at *n* and *o*, and similar delicate bodies were often seen free, commonly in pairs, as represented in the series *l*, *p*, *q*, *r*. Of these, *l* resembles in its thicker half a very young plant such as *m*, while its more slender portion corresponds with *p*. This again, as well as the still more delicate *q* and *r*, seemed to be neither more nor less than bacteria, as was shown not only by their form, but by the fact that precisely similar bodies were not unfrequently seen exhibiting active and perfectly characteristic movements. Further, there were many motionless bodies, such as *s*, which previous experience enabled me to recognise as young bacteria multiplying by segmentation, while they were fully equal in thickness to sprouts, such as *o*, proceeding from the filaments. The identity of the bacteria with the filaments was further indicated by the precise similarity of the delicate transverse markings often observed in the former (as in *p* and *r*) with those of young plants, such as *m*.

That bacteria should originate from filamentous fungi was an idea entirely opposed to the preconceived notions with which I entered upon this inquiry; for, in common with those authorities on the subject whose observations appeared entitled to greatest weight, I had regarded these organisms as a separate and altogether distinct group. But the contrary conclusion was forced upon me not only by the observation which I am now recording, but by various others, some of which will be described in the sequel. I need hardly remark that, if correct, it is of the very highest interest.

In the present instance it is certain that the bacteria moving in the liquid were identical, morphologically, with buds derived from the fungus; and this fact receives additional weight from the circumstance that the glass had been left untouched for seven months, having been previously securely guarded against the entrance of organisms from without; and even if bacteria, as such, had been accidentally introduced when the vessel was last exposed, it is in the highest degree improbable that they would have remained in an active condition for such a protracted period. If, therefore, we set aside the idea of spontaneous generation, which I trust before this paper is concluded the reader will see that we are justified in doing, it is difficult to conceive how these bacteria could have arisen, except from a gradual alteration in the character of the original organism under the influence of progressive changes in the medium which it inhabited.[1]

[1] It is indeed conceivable that a bacterium incapable of growing in fresh urine may have lain

I next proceeded to examine the Pasteur's solution. The liquid was still perfectly transparent and colourless, contrasting remarkably with the jet-black colour which I had observed to result in a much shorter period from the action of yeast upon the same fluid.[1] There was, however, a good deal of white deposit, partly in the form of a loose sediment, partly as a delicate incrustation upon the side of the tube, and some white patches were floating free, probably in consequence of the disturbance of the vessel: there was also a little scum on the surface. Only about a sixth part of the liquid had evaporated; and, as before mentioned, the part of the glass which had been left dry was studded over with little gelatinous bodies like those in the tube of urine. The tube being longer in the present case, I failed to pick out any of those little bodies with a needle. I was therefore obliged to content myself with examining a drop taken with 'heated' pipette from the upper part of the liquid, including some of the white floating particles. These, however, proved all that I could desire, being composed of the same organism that I had found in the urine, and all the better seen because it had not been disturbed by the needle. *b*, *c*, and *d* of Plate VII represent three entire plants, of which *b* fully equals in slenderness any seen in the urine; and some idea of its exquisite delicacy may be given by saying that ten such threads might lie abreast in the diameter of a single red corpuscle of human blood. *d* is introduced as a good example of the production by such filamentous plants of substantial conidia having the characters of the cells of *Torula Ovalis*, while in *c* we have a plant which in some parts is as delicate as *b*, while in others it looks as if composed of elongated cells of the torula. Other obviously transitional forms between the filamentous fungus and the torula are represented by the groups *e*, *f*, and *g*. Comparing the appearances of the organism as it occurred in the two glasses, the cellular element predominated over the filamentous in the Pasteur's solution, while the converse was the case in the urine. The toruloid groups, rare in the latter liquid, were abundant in the former, in which also the filamentous plants were as a rule of a coarser character, and were invariably small; that is to say, not extending to any great length, as they did in the other medium. The granules of the filaments and the nuclei of the cells were also much more marked in the Pasteur's solution. Along with this deficiency of the filamentous element, the bacteric form was absent in the Pasteur's solution. Some of the buds were indeed as slender

dormant in the liquid till it had become so altered under the influence of the torula as to be a suitable nidus for it. Meanwhile the fact of the morphological identity of this bacterium with buds from the filamentous fungus must be taken for what it is worth.

[1] I am not prepared to say whether the black colour which I have invariably found to be caused by the prolonged action of yeast upon Pasteur's solution is due to the *Torula Cerevisiae* or to other organisms accompanying it.

as the bacteria of the urine, as is illustrated by the plants *b* and *c*, and here and there such buds were seen floating free in pairs such as *h*, but no bacteric movement was to be seen. This puzzled me at the time; but I afterwards found that it was no reason for surprise, and I shall hereafter have occasion to mention cases of bacteria of ordinary form and active movement in urine, assuming a motionless character and at the same time a very different appearance in other media.

Although the proof already afforded of the identity of the *Torula Ovalis* with the filamentous fungus may appear sufficiently ample, yet, as the point is of extreme interest, I have been well pleased to obtain further confirmation of the fact while preparing this communication for the press. On the 9th of November, 1873, I once more removed the test-tube containing the Pasteur's solution from its cotton packing to see what change it might have undergone. I found about half of the original volume of the liquid still remaining unevaporated. It was still transparent, but it was now of a pale brownish-yellow colour, and the sediment had a similar tint. A delicate incrustation existed on the interior of the glass, but did not reach up to the level of the liquid, and the gelatinous lumps had disappeared from the dried part above. Raising the test-tube cover with careful antiseptic precautions, I removed a few drops, taking up at the same time a little of the crust, which I detached from the side with the 'heated' pipette; and, after inoculating a glass of Pasteur's solution with about half a minim, I proceeded to investigate the remainder. Under the microscope the solid constituent proved to be composed in the main of granular masses, looking like confused aggregations of the organism in an effete and degenerate state; but projecting from the edges of these masses were plants and corpuscles, which, from their translucent and fresh appearance, made me hope that they were alive. The filaments closely resembled those seen in this glass a year and a quarter before, except that they were invariably very short, and the corpuscles, while sometimes in groups more or less resembling the original torula, were often of a more elongated form and strongly nucleated. During the first five days after the inoculation there was no distinct appearance to the naked eye of any growth taking place in the new glass of Pasteur's solution. At the end of that time, however, thinking that a speck of delicate scum, which existed from the first, appeared slightly increased, I examined a portion microscopically, and found it to consist entirely of cells which appeared of new formation, some of them presenting transitional forms between the elongated bodies common in the test-tube and the constituents of the oval torula. The growth afterwards continued, both as a very delicate scum, and as a fine white deposit; but its rate was extremely slow, and the product for the most part on a much smaller scale than the original torula, and more resembling the elements found in the test-tube.

Very different was the behaviour of the organism in unaltered urine. Two days after the inoculation of the Pasteur's solution, I introduced half a minim of the liquid from the test-tube into a 'heated' and covered glass, containing unboiled urine from a flask which had been charged on the first of March, but, though it had furnished the material for many successive experiments, retained its original characters unimpaired.[1] For two days there was no appearance of growth; but on the third day a small patch of scum, which had been the immediate result of the inoculation, was considerably increased in size, and had acquired a much coarser character, and several small detached specks of similar aspect were floating on the surface. The side of the glass was also sprinkled with minute particles like grains of white sand, often disposed in vertical streaks, while other similar granules were deposited at the bottom, the liquid retaining its brilliant clearness. In short, the naked-eye appearances were an almost exact reproduction of those which resulted from the introduction of the rain drops into the original urine nearly two years before, and on applying the microscope to a portion of the scum taken up with 'heated' pipette, I was delighted to find it composed exclusively of the *Torula Ovalis* in all its original beauty, the constituents cells pullulating freely, as shown at *i*, Plate VII, which represents, for convenience of sketching, a small specimen of the groups, which were commonly much larger, like those of the yeast plant when in full activity. In some fields the cells were peculiarly large, as at *m*, and here and there, as at *l* and *n*, a cell was somewhat longer than usual, just as occurs in *Torula Cerevisiae*; but there was no appearance of filamentous growth. It was a torula pure and unmixed; yet its identity with the *Torula Ovalis* and its distinction from the yeast plant were declared not only by the form and aspect of the cells, but still more by the fact that, just like the original specimen, it grew freely in non-saccharine urine, in which *Torula Cerevisiae* develops only with extreme difficulty.

The organism, having thus, after many months of slow growth in the filamentous form in the altered Pasteur's solution, recovered its purely toruloid and luxuriant habit in the medium in which it presented those characters at the outset, retained them when transferred to uncontaminated Pasteur's solution. For having, with the touch of a 'heated' pipette, introduced a speck of the rapidly growing scum from the urine into a second glass of Pasteur's solution, which had been charged along with the former six days before, but had hitherto

[1] The method by which this flask was prepared, and the mode of decanting into the experimental glasses, will be described in a later part of this paper.

remained unchanged, I found the morsel of scum increased in fourteen hours to four times its original diameter, and on the following day it nearly covered the surface of the liquid, and the side of the glass was sprinkled with white granular specks, which after another day were disposed in vertical streaks, just as they had been in a glass of Pasteur's solution inoculated from the original urine-glass nearly two years previously. And on examining the scum microscopically, I found it to consist of the torula unmixed with any filamentous element, as seen in *o, p, q, r,* and *s,* Plate VII.

Those who have the patience to follow me through these minute details, inseparable from so minute a subject, will acknowledge the importance of having it clearly demonstrated that an organism, which, for weeks together and in different media, showed itself as an unmixed torula, was in reality a conidial development from a filamentous fungus. For one such instance rigorously proved, leads to the suspicion that the same is in all probability the case with the whole group of torulae, and that though Berkeley appears to have been deceived when he thought he traced a direct connexion between *Torula Cerevisiae* and *Penicillium Glaucum*,[1] yet his belief that the yeast plant is derived from some filamentous form will turn out to have been sound when the mode of investigation which I have been describing shall have been applied to that case. Without some such method, permitting us to study an organism for a protracted period, unmixed with others, in different media or in the same medium altered under its fermenting influence, the true affinities of the *Torula Ovalis* would have remained as obscure as those of *Torula Cerevisiae* are at present. Further, without entering here upon all the bearings of this observation, it may be remarked that for an organism so humble as a torula, though modified by varying circumstances, to retain its specific morphological and physiological characters unimpaired for two years together, is a fact fraught with the deepest instruction.

I next unpacked and examined the test-tube containing the urine. I found the fluid all evaporated except about two minims above a considerable crystalline mass. The part of the glass, about an inch high, left exposed by the drying was studded over as before with round gelatinous specks, those on the upper half-inch being largest, viz. about 1-50th inch in diameter. Breaking the tube with antiseptic precautions, I examined one of the little transparent lumps with the microscope, and found it to consist almost exclusively of the filamentous form of the fungus, the conidial element being, as before, much less marked in this tube than in that of Pasteur's solution. There was a somewhat larger proportion of conidia in the liquid residue, which, however, was thick from the abundance of the fungus filaments in it ; but there was no longer any appear-

[1] See de Bary, *Morphologie und Physiologie der Pilze*, &c., Leipzig, 1866, p. 184.

ance of bacteria. I introduced a portion of the gelatinous lump into a glass of uncontaminated urine, which had been charged along with the one inoculated from the tube of Pasteur's solution (viz. nine days previously) ; but as no growth showed itself in the course of the next eleven days, I concluded that the organism had, in the highly concentrated and altered urine, at length lost its vitality. Yet the examination of this urine-tube proved not devoid of interest. For although the bacteria which were seen in it when it was last examined had the ordinary rod shape, and did not differ in appearance from those commonly seen in putrefying urine, yet the liquid in this glass had no ammoniacal odour, but a very peculiar smell resembling musty cheese rather than urine, and it was sharply acid to test-paper, even when diluted with several times its bulk of water. Here, then, we have an example of what we shall see abundantly illustrated in the sequel, viz. that bacteria of similar morphological characters may differ entirely as regards the fermentative changes to which they give rise, being, like the torulae, as specifically distinct as the fungi from which some of them at least appear to take their origin.

The observations to which I have next to direct attention were made upon a filamentous fungus, which I was induced to investigate in the hope that it might prove to be the parent of the *Torula Cerevisiae,* occurring as it did in circumstances analogous to those under which the filamentous form of the *Torula Ovalis* had been met with. I had introduced into a ' heated ' and covered glass of Pasteur's solution a morsel of German yeast, with the effect of inducing the usual evolution of gas that accompanies the alcoholic fermentation, followed by the gradual supervention of the black colour before alluded to. Some minute plants of filamentous fungi, seen in the course of the first few days, had apparently ceased to grow, and no penicillium or other ordinary fungus appeared ; but after the lapse of two months I observed, upon the surface of the liquid and upon the part of the glass left exposed by evaporation, a low white mould, which, under the microscope, was seen to be composed of branching septate filaments and fructifying threads, the latter in somewhat irregular forms, but most frequently producing moniliform terminal chains of spores ; the fungus, though apparently too insignificant to have attracted the notice of mycologists, being referable to the genus oidium. The largest of the spores were not unlike those of yeast ; and other similar spores were seen in toruloid groups in the scum that existed on the surface of the liquid. Hoping that I had discovered the filamentous form of the *Torula Cerevisiae,* I was anxious to investigate this mould further ; but having used all the scanty growth for the examination already made, I set the glass aside to allow further development, and circumstances prevented me from looking at it again till nearly four months more had elapsed. I then found the sour liquid blacker than ever, and further reduced by evaporation, the only other change visible to the naked eye being that the same low white mould had grown again in small amount upon the side of the glass. Finding that it still retained the same characters under the microscope, I hoped that by transferring it to a saccharine solution I might get it to reproduce the *Torula Cerevisiae*, just as I had got back the *Torula Ovalis* by placing its filamentous form in fresh urine. Accordingly, having taken up a portion of the mould with a 'heated' knife, I introduced a morsel of it into a 'heated' and covered glass containing freshly prepared Pasteur's solution, and placing the remainder in a drop of water between plates of glass, made a further examination with the microscope. a_1 in Plate VIII represents a fructifying filament, the segments of which are some of them in the form of a moniliform chain of spores, while others present a transverse line indicating tomiparous division into gemmae, and one has given off a conidial bud, the last being an appearance comparatively rarely seen in this fungus when first removed from the wine-glass. But on examining again, after fifteen hours, the same specimen, which had been kept in a moist atmosphere to prevent evaporation, I found free spores in considerable numbers about the filament previously sketched, and the filament itself was studded with numerous fresh conidial buds, as shown in outline at a_2, the one previously present having dropped off. The great rapidity with which this conidial budding took place under the influence of the water is further indicated by the sketch at a_3 taken only two hours later, where all the buds present at the former examination are seen to have either grown larger or to have dropped off, while several fresh ones have made their appearance.

This abundant formation of conidia in the new medium increased my hopes that I should get back the *Torula Cerevisiae* in a saccharine fluid. This hope, however, was doomed to disappointment. So far from the organism exhibiting in the glass of Pasteur's solution a toruloid development, it assumed there the opposite condition of a filamentous growth, in which any appearance of conidial formation was a rare occurrence. *b*, *c*, and *d* in Plate VIII represent sprouting conidia, *e* a very young plant, and *f* the extremity of a filament. The entire distinction of this fungus from the yeast plant was further shown physiologically by the fact that it grew extremely slowly in the saccharine liquid, and failed to cause any evolution of gas in it, though kept under observation more than two months. I was thus led to conclude that this oidium had been merely an accidental concomitant of the yeast plant, having sprung, perhaps, from one of the adventitious filamentous plants noticed during the first few days in the glass, and having survived the chemical changes in the fermenting liquid under which the yeast plant itself had succumbed.

But though disappointed of the results which I had hoped to have obtained from this oidium, I made some other observations upon it which proved to be of considerable interest. The remarkable conidial development which took place from it in water seemed such a striking instance of change of habit in the plant induced by a new medium, that I thought it worth while to try what effect would be produced upon it by various other liquids, and among the rest by unboiled and uncontaminated urine; and on the 21st of August, 1872, I introduced into one of a series of 'heated' and covered glasses of that fluid, prepared on the 10th of the month, and as yet unaltered, a minute portion of the organism from the glass of fresh Pasteur's solution, where, as before mentioned, it was growing slowly in a filamentous condition; the delicate threads becoming broken up in the process, and diffused in an invisible form in the liquid. At the same time, for the sake of comparison, I inoculated from the same source another glass of Pasteur's solution, as well as other liquids to which I need not here allude. In the fresh glass of Pasteur's solution the growth proceeded, as in the previous one, in the form of branched and septate filaments, one of which is represented in outline at *g*, Plate VIII, on a smaller scale than the rest of the plate, while *g′* gives in detail a portion of the same filament as seen under the usual higher power: and in the course of two days the naked eye detected white specks upon the side of the glass, which the pocket-lens showed as little woolly tufts. Meanwhile, in the urine the glass had also become sprinkled with white specks, but under the pocket-magnifier, while some of them were filamentous, as in the Pasteur's solution, many presented a granular appearance.

In examining the growth microscopically, I availed myself of an arrangement which I have often found advantageous. At the time of inoculation I had introduced into the urine a small plate of glass, with pieces of fine silver wire connected with its ends in the form of hooks, by which it could be suspended from the rim of the glass; so that, lying horizontally in the liquid, it might arrest as they fell organisms diffused through it. The little apparatus had of course been previously purified by heat. Such a plate being carefully removed with 'heated' forceps after development has advanced to any desired degree, and covered with a slip of thin glass, permits the examination of any growth that may have formed upon it, in a comparatively undisturbed condition. Thus, in the present instance, I was enabled to see *in situ* with the microscope the plants which the pocket magnifier had revealed. Under a low power they presented appearances such as are shown at *a*, *b*, and *c*, Plate IX, *a* being a purely filamentous growth, *c* a granular group, and *b* one exhibiting both characters in combination. Under the high power the granular parts were found to be composed either of groups of free pullulating cells of oval form, generally disposed in pairs, as shown at *c*, Plate IX, or of plants of a most imperfect description, consisting of cells of a similar character to the free ones, or slightly more elongated, connected end to end, and often producing conidial buds, as in the specimen figured at *d* in the same plate.

On the following day the difference between the two glasses was still more marked. The filamentous plants in the Pasteur's solution had considerably increased, but those in the urine had almost all fallen to the bottom, their places being taken by abundant specks and streaks of granular aspect, and even the few plants that still remained adhering had lost their purely filamentous character and had become granular. There were also little patches of scum upon the urine, whereas the surface of the Pasteur's solution presented only some floating filamentous plants. I removed a portion of the scum with 'heated' pipette, and submitted it to the microscope, and found it to consist exclusively of free oval cells, like those seen in the granular specks the day before, as shown in outline at *f*. In the course of the next twenty-four hours all appearance of filamentous growth disappeared from the urine ; but while the liquid, which was now for the first time observed to have a slightly offensive smell, had become unsuited for that mode of development of the organism, it had stimulated the corpuscular form in a most remarkable manner, the scum having increased with amazing rapidity. Thus, between 8 p.m. on the 24th and 5.30 a.m. on the 25th, it grew from a loose patch, about half an inch in diameter, to a dense film that covered almost the entire surface of the liquid in the urine-glass, and eight hours later, the cell growth had been so great that the scum had become pushed up upon the glass to about a quarter of an inch above the level of the liquid, while the urine was rendered cloudy by the subsidence of detached cells. In the course of the afternoon the liquid had become turbid throughout, and the air in the glass shade was still more decidedly offensive ; yet, under the microscope, the only organism discoverable was that represented by the pairs of cells before described, so that we have here another clear example of fermentative change of putrefactive character induced in urine by other agency than bacteria. Samples of the cells are given in *g*, Plate IX, where they are seen to resemble those of *d* and *e* in having vacuoles, but no nuclei, merely, in some cases, inconspicuous granules. In *g* is also given in outline a portion of the scum, showing how densely packed the constituent cells were, corresponding with the remarkable naked-eye appearance, which was that of a dense white layer, like a film of paraffin.

On the same day (August 25), I introduced a small portion of this scum into a second glass of urine, prepared along with the former one fifteen days previously, but as yet retaining its brilliant clearness, and in other respects also unaltered, the transference being effected by a touch with the tip of a slender glass rod previously 'heated'. The results of this inoculation differed from those seen in the former glass of urine in this, that no filamentous plants at all now made their appearance, while, on the other hand, the corpuscular mode of development proceeded with great rapidity. Thus, eight hours after the inoculation, the side of the glass already presented streaks having a granular aspect under a pocket-lens, and a portion of scum which had remained at the surface had increased to four times its original extent, presenting the same dense white character as in the former glass, like a film of wax or paraffin. I examined a portion of the scum microscopically, and found it to consist in the main of cells, free or in pairs, formed by pullulation, as shown (for the most part in outline) in the sketch given at *i*, Plate IX. But there was besides frequently seen an appearance of somewhat longer sprouts, like an abortive attempt at the formation of filamentous plants, of which also specimens are given in the sketch *i*. Twelve hours later the inside of the glass looked as if sprinkled over with coarse white sand, while the scum had grown so rapidly as to be more than eight times as large as when last observed. A portion of scum is represented in outline at *k*, where it is seen that there is no longer any appearance of long sprouts, the filamentous tendency having entirely disappeared, while the constituent cells are of smaller dimensions than before. Another point of much interest was the fact, that now, within twenty-four hours of the inoculation, the liquid, which, when inoculated, had the odour of perfectly fresh urine, was already markedly offensive; and after the lapse of twenty-four hours, while the scum had almost covered the surface of the liquid, the rank smell was strong. Now it may be remembered that in the former glass no offensive smell was observed during the first three days, though the filamentous growth had proceeded luxuriantly, and that it was only after four days, when the filamentous form had given place to the corpuscular and the scum had made its appearance, that the rank odour was perceived. Hence we are led to infer that the same organism may differ in its effects as a fermentative agent according to its habit, the toruloid form in the present instance being a much more energetic ferment than the filamentous. I had the opportunity of verifying this observation seventeen days later, when another glass of urine being inoculated with the same scum, there was again a rank smell in twenty-four hours.

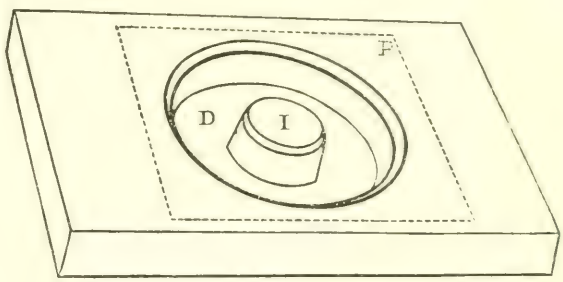
But to return to the glass under consideration. On the 27th of August, two days after inoculation, it stank as strongly as the first glass; and now on examining a portion of the scum with the microscope, I was surprised to find a very remarkable change in its constituent cells, which, instead of being oval bodies with mere vacuoles and inconspicuous granules, and either free or in pairs, were now of spherical form destitute of vacuoles, but strongly nucleated, as shown at *l*, Plate IX, and disposed in considerable irregular groups, as seen in the outline portions of the sketch. The same character was maintained by the scum in this glass during the rest of the time (fifteen days) that it was kept under observation, *m* being a sketch of its appearance after the lapse of ten days ; so that the organism had assumed completely the appearance of a spherical torula.

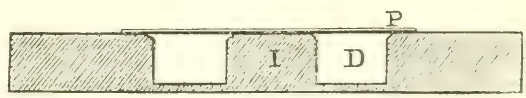
But it may be asked, Was I not deceived in supposing that the new toruloid form in the second inoculated glass had anything to do with the oidium ? May it not have been a totally different species accidentally present, just as the oidium itself was apparently adventitious in the yeast-glass ? That all the oval cells should have disappeared within twenty-four hours, and given place to another species producing a scum of the same remarkable naked-eye appearance, seemed indeed very improbable ; but, on the other hand, the difference of character in the cells was so remarkable, that if it was really only due to a modification of the same organism, it was desirable, if possible, to place the fact beyond doubt. With this object, on the 30th of August, I mingled a morsel of the scum, by means of a 'heated' glass rod, with a drop of Pasteur's solution[1] on a 'heated' slip of glass, and placed upon it a 'heated' piece of thin covering glass, and over this a larger plate of thin glass also 'heated', overlapping the former one well on all sides, and luted down the margins of the upper glass with melted paraffin, applied with a hot steel pen. The object of this arrangement was that, while evaporation should be prevented by the paraffin luting, the interval between the thin glass plates might contain a supply of air to permit the growth of the fungus. I then selected for observation a group of the spherical cells near the edge of the liquid, and therefore near the air between the plates, and sketched them with camera lucida, as shown at n_1, Plate IX. This was at 5.50 p.m. At 6.8 p.m., I noticed a change in the nuclei of the cells, such as I have often observed in spores preliminary to germination, as indicated at n_2, and by 11 p.m., the object being still undisturbed under the microscope, the lowest of the cells had not only increased in size, but had produced a considerable elongated sprout (see n_3), while the other cells were all markedly changed in the character of their nuclei. At midnight the sprout from the lowest cell had itself produced another sprout, also of oval form (see n_4), and by 7.45 next morning, when I next looked at the object, two other cells had been produced from the last sprout, while some, if not all the other cells of the group, had also germinated, giving rise to the appearance shown at n_5. And it will be observed that the products of this growth of the cells of the scum were not spherical and nucleated like them,

[1] The Pasteur's solution contained 1 per cent. of alcohol, for reasons with which I need not trouble the reader.

but had the oval and vacuoled character of the scum of the earlier period, so that the specific identity of the two growths was no longer doubtful.

I afterwards obtained still more satisfactory evidence on the same point. The long sprouts observed in the scum of the second glass of urine, a few hours after inoculation, seemed to indicate that the very liquid which, when altered by fermentation, induced the change of the organism to the toruloid condition, favoured, when perfectly fresh, a return to the filamentous form. I therefore resolved to watch, if possible, the earliest growth of the spherical cells of the scum in uncontaminated urine. For this purpose I proceeded on the same principle as before; but experience having shown that the thin layer of atmosphere between the glass plates was exhausted within a few hours, I tried a new arrangement for providing a larger supply of air, that which I ultimately arrived at being as follows:—A piece of plate-glass about three-eighths of an inch thick, and about $2\frac{1}{2}$ inches by $1\frac{1}{2}$ in the other dimensions (shown in diagram in the accompanying woodcuts, the lower of which represents it in section), is excavated by the lapidary into a circular ditch, D, round a central island, I, the island being three-eighths of an inch in diameter, and the ditch or air-chamber of about the same breadth, and as deep as the thickness of the glass will conveniently permit, viz. about a quarter of an inch. A piece of thin covering glass, P, sufficiently large to cover the ditch as well as the island, but not quite so broad as the glass plate, so that it can be conveniently sealed down with paraffin, completes the ‘glass garden’, which is stocked as follows:—The glasses must first be heated and allowed to cool, without access of dust to the air-chamber. The glass plate with the cover *in situ*, and covered further with a larger slip of ordinary glass, is placed upon a broad plate of metal on a retort stand, and over this a metal lid, such as that of a tin biscuit-box. Heat is then applied to the metallic plate by means of a Bunsen's burner or large spirit-lamp, till a drop of water sprinkled on the tin lid above passes off at once by ebullition. The lamp is then removed, and cooling is allowed to take place completely. The object of the metal plate and lid is to diffuse the heat, and thus prevent cracking of the thick and irregularly shaped plate of glass. The lid above aids in keeping out dust during cooling, and this is further effected by the thin covering glass and the overlapping





glass slip above that. This slip is also useful in the stocking of the glass garden. Having been taken up from the other glasses, it is placed inverted on the table, so that the surface which was downwards during the cooling, and therefore free from dust, may be directed upwards. A few drops of the new liquid medium, in which development is intended to occur, are then placed upon it with 'heated' pipette, and to these a minute portion of the organism is added and diffused thoroughly among the fluid by stirring with a 'heated' glass rod. The thin covering glass being now raised by means of 'heated' forceps, aided in the manipulations by a 'heated' needle, a very small drop of the mixture of organism and medium is placed, by means of the pipette, upon the central island of the garden, and, in order to ensure a moist atmosphere in the air-chamber, a drop of water, which has been boiled, and cooled under protection from dust, is introduced with a clean 'heated' pipette into the ditch.[1] The thin covering glass, which has been still held in the purified forceps, is then accurately replaced, after which its margins are luted down with paraffin, which is conveniently melted in an egg-spoon, and applied with a clean steel pen heated from time to time in the spirit-lamp. This process requires considerable delicacy and quickness of manipulation, and constant watchfulness; but with these conditions it may be conducted with most satisfactory results; and I have watched one and the same organism continuing to grow unmixed in such a garden for several weeks together, though carried about with me in a journey made in an autumn holiday.

As soon as the stocking of the garden is completed, it is placed under the microscope, and some individual specimens of the organism are sketched by camera lucida—a map, on a smaller scale, being also made with the camera to enable the observer to find the objects again.

On the 11th of September I stocked such a garden with a little of the scum from the second urine-glass, mixed with uncontaminated urine from one of the glasses charged on the 10th of August, the liquid still retaining its original brightness and fresh odour. The cells of the scum thus introduced between the island and the covering glass were all of the spherical character, as is illustrated by the groups at *a* in Plate X, sketched at 7.20 p.m., within a few minutes of their

[1] The actual order of proceeding is to introduce the boiled water into the air-chamber first, after which the same pipette, being clean, may be at once used for the liquid medium. I have found the most convenient form of pipette for these experiments to be a small syringe, having its nozzle connected, by means of a short piece of caoutchouc tubing, with a glass tube very narrow and thin, so that it is almost instantaneously heated nearly to redness by passing it through a flame, and cools with corresponding rapidity. The tube is bent near its middle at about a right angle; so that neither the syringe nor the hand is held over the experimental glass, while the yielding nature of the caoutchouc junction allows the end of the glass tube to be pressed, without risk of breaking, against any object, such as the side of a wine-glass, from which an organism is being picked up.

introduction. At 9.50 p.m. the nuclei were found more conspicuous and altered in position, but there was as yet no change of form in the cells. Early next morning I found that the cells generally were sprouting ; but it happened that those which I had drawn had shifted their position slightly, so that I could not distinguish them in their now altered shape from others in their vicinity, but I selected two groups for further observation, represented at b_1 and c_1, sketched at 1.30 and 1.35 a.m. respectively. It will be observed that, while this early stage of germination has changed them from the spherical to an oval form, they still retain their nucleated character. Five hours later, growth had advanced in both groups so as to give the appearance represented at b_2 and c_2. In both groups the nuclei have almost disappeared, while the sprouts have much increased ; and in c_2, while the highest of the three cells has produced a short filament, the lowest has formed two oval vacuoled cells, and the other, after growing an oval cell, has gone on to the development of a short filament.

After four more hours had passed, I was rejoiced to find the experiment crowned with complete success. The longer sprouts of c_2 had become extended to threads of considerable length, as represented in c_3 ; while the progeny of the other original cell was in the form of pairs of oval vacuoled bodies destitute of nuclei, exactly resembling the constituents of the first scum, or of the granular deposits which accompanied the woolly tufts on the first urine-glass. And just as in that glass, at an early period, some plants exhibited the filamentous others the corpusclar form of growth, so was it with the offspring of the three spherical cells whose development we have followed.

Such was the effect of uncontaminated urine upon this organism. Afterwards, however, as the liquid gradually became vitiated under its fermenting influence, the filamentous form of growth which first appeared began to give place again to the corpuscular, a change which the ‘ glass garden ’ afforded opportunity of watching with perfect precision. c_4 shows the lower of the two filaments of c_3 at 5.50 p.m. on the same day, represented on a smaller scale. It will be observed, that, while the filament has increased considerably in length, it exhibits a tendency to break up into segments, and here and there along its course it has produced oval corpuscles. And a further progress of the same alteration of habit is exhibited in c_5, where the same filament is again sketched on the same scale after the lapse of ten hours more, viz. at 3.50 a.m. on the 13th of September. The filament has only increased very slightly in length, but the terminal portion has broken up into segments, and assumed a zigzag form in consequence, while a multitude of corpuscles have been produced in the course of the filament, partly by budding of the segments of the thread, and partly by the pullulation of the corpuscles themselves, many of which are already of the spherical form. And the spherical cells, when examined with a high power, were found to be nucleated like those of the last scum. Here and there a plant was found in which, in consequence, I presume, of greater vigour, the filamentous growth had proceeded further before the corpuscular development occurred, and formed septate branches, reproducing exactly the original filamentous form of the organism. This is illustrated by *d*, which represents part of another plant, drawn under the high power in the evening of the same day, and introduced not only on account of the delicate septate branch which it presented, but because nucleated spherical cells were seen to spring directly from little stalks on the thicker portion.

Next day I found one plant so beautifully illustrative of the whole subject that I took a sketch of it, which is represented at *e*, Plate X, the drawing being on a much smaller scale, to enable me to include the whole. The plant had sprung from a spore situated not far from the edge of the island, and had grown towards the air-chamber, and, arriving there, had continued to spread itself upon the under surface of the thin glass that formed the roof of the chamber. It will be observed that the part of the plant which is most distant from the air-chamber has assumed the zigzag form resulting from a tendency to break up into segments, and has produced a considerable number of spherical spores. Nearer to the air, again, the plant retains its original form, and has very few conidia ; while the part in the air-chamber presents the characters of a branched filamentous fungus entirely destitute of conidial formation, and this in the very same plant which in another part of its course has the loosely jointed character with spherical spores.

But how were these differences in different parts of the plant to be explained ? Why did the portion in the air-chamber retain the purely filamentous and compact character, while the part on the island and other plants situated there became broken up, and produced conidia ? The conidial development upon the island could not be the result of deficiency of oxygen ; for this mode of growth occurred in greatest profusion in the scum of the urine-glass, which was freely exposed to air which was being constantly changed. And in point of fact, the air in the glass garden was not nearly exhausted at this period ; for on examining it again on the 3rd of October, I found that the filamentous form of the fungus had by that time grown rampantly over the roof of the air-chamber, and had even grown down its walls in some places, and spread upon its floor. The obvious explanation appeared to me to be, that the agent which exercised the modifying influence upon the growth of the organism was some volatile product of fermentation, probably that which assailed the nostrils with a pungent stink, and that, where it was evolved in a limited space confined between the two plates of glass, it accumulated and produced its effect upon the plants. When, on the other hand, it was formed in the very thin film of liquid, which alone accompanied the plant on the roof of the air-chamber, it escaped into the air as fast as it was produced, and left the fungus unchanged. And this view is strongly confirmed by another fact, which I observed at the time when the glass garden was stocked (on the 11th of September), viz. that in the first urine-glass the filamentous form of growth, which had been entirely suspended four days after inoculation, was again present in abundance, forming little woolly tufts, which studded the side of the glass. In other words, the urine had been restored to a condition compatible with the filamentous mode of development; and the natural explanation of this occurrence is, that the substance which exerted the modifying influence upon the organism, stimulating the corpuscular while checking the filamentous formation, was a volatile product of fermentation of some constituent of the liquid present in limited amount, and that when this constituent was exhausted, and the volatile product had escaped, the organism was again at liberty to form filaments, as it would have done if placed in fresh urine.

The investigation with the 'glass garden' had thus abundantly proved that the filamentous fungus seen in the glass of Pasteur's solution, the pairs of oval vacuoled corpuscles of the primary scum in urine, and the spherical nucleated cells of a later period, were one and the same organism, modified by circumstances; while in the last-named variety we have another example of a plant presenting for weeks together the character of a pure and unmixed torula, which, had I seen it only in that condition, I should have considered as much entitled to that generic name as the yeast plant, yet rigidly demonstrated to be a conidial development of a filamentous form. Comparing it with the *Torula Ovalis*, there is this curious difference between them, that whereas in the latter fresh urine is a medium in which the toruloid form especially flourishes, the filamentous growth making its appearance in it only when the liquid has been altered by the fermenting influence of the organism, the converse is the case with this plant. The present species, like the *Torula Ovalis*, failed to effect the ammoniacal fermentation of urea, the contents of the second urine-glass being found still sharply acid on the 5th of November, ten weeks after inoculation. Yet it is, as we have seen, an energetic putrefactive ferment of some of the urinary constituents, and on this account is attended with considerable interest. And as the remarkable naked-eye appearance of the scum which it forms in that liquid when altered under its agency, and the toruloid character of the constituent cells, appear to furnish sufficiently definite specific characters, it seems desirable that it should be named, and I have suggested for it the title *Oidium Toruloides*.

Some other points observed in the investigation of this plant appear of sufficient interest to be placed on record. One is, that the spherical toruloid cells of the scum of the second urine-glass, when introduced into a fresh glass of Pasteur's solution, produced none of the purely filamentous growth such as resulted from the inoculation of the two previous glasses of that liquid with the filamentous form of the organism, any threads met with being only of a very loose and imperfect character, like that represented at *d*, Plate IX, while the chief product of the development was pairs of oval vacuoled corpuscles, resembling those of the scum of the urine at an early period. And the result was not only a granular deposit on the side of the glass, but a scum upon the surface, whereas neither of the other glasses of Pasteur's solution had shown any scum. This difference between the glasses continued as long as they were kept under observation ; that inoculated with the toruloid scum still presenting a growth mainly of scum, without any filamentous appearance visible to the naked eye till the 14th of September, eighteen days after inoculation, while the other two glasses had still no scum whatever, and exhibited abundant conspicuous woolly tufts. This fact is of itself proof of a very important general truth, viz. that a particular habit of growth impressed upon an organism by temporary residence in a new medium may sometimes be retained for a long period after it has been restored to its former habitat. The effect of the stale urine upon this plant was to substitute the corpuscular for the filamentous mode of development ; and although, when returned to the Pasteur's solution, there was a degree of recovery, as indicated by the change from the spherical nucleated cells to the oval vacuoled corpuscles, and still more by the occasional appearance of coarse imperfect threads, yet the original character was not restored during the eighteen days of observation. And this circumstance is the more interesting, when it is remembered that the corpuscular variety appeared to differ from the filamentous in fermentative power, the former being more energetic in its effects on urine than the latter. Facts of this kind may tend to elucidate points of great importance in the history of contagious diseases, such as the greater virulence of such disorders at some periods than at others. For it seems highly probable from analogy that the *materies morbi* may be of the nature of minute organisms ; and if this be the case, we can understand, from what we have seen of the plant under consideration, that differences of energy in the virus may be occasioned by varying circumstances.

The failure of the plant to resume the filamentous habit when returned to Pasteur's solution, makes it the more remarkable that it should have recovered that power in fresh urine, implying that this secretion, when in a perfectly unaltered condition, is a still more favourable medium for the organism, permitting a degree of recovery which was impossible in Pasteur's fluid.

The last fact which I have to mention regarding this plant, is its behaviour in an albuminous liquid. This medium, which also proved valuable in experiments to be described in a later part of this paper, was prepared on the same principle as the unboiled urine, by taking the material uncontaminated from its natural receptacle, by aid of antiseptic measures. An egg, known to have been laid within the last twenty-four hours, was steeped for a while [1] in a solution of carbolic acid in twenty parts of water, to destroy any organisms adhering to the shell, and was then broken in a fine spray of carbolic-acid solution of the same strength, and about an ounce of the white of the egg was introduced into a flask containing ten ounces of water, which had been boiled and allowed to cool, the air which entered during cooling having been filtered of dust by a mass of cotton-wool tied tightly over the mouth of the vessel before boiling. The flask was agitated occasionally during the next twenty-four hours, to promote diffusion of the albumen in the water, after which the liquid was passed through a boiled filter placed in a 'heated' funnel, protected with a 'heated' glass cover, under a large glass shade.[2] It was thus cleared of the shreddy residue of the white of egg, and also of the opaque floccules resulting from the action of the carbolic-acid spray upon the albumen, and was obtained of crystal clearness in the 'heated' flask into which it was received, and in which it was kept protected from dust by a 'heated' glass cap and a glass shade. A 'heated' wine-glass, provided with cover and glass shade as usual, being charged with some of this liquid, I inoculated it with a little of the toruloid scum from the second wine-glass on the 3rd of September. The result was a corpuscular development of a delicate inconspicuous character, the growth proceeding so slowly that the little patch of scum, in which alone any increase was observed, had not doubled its diameter in ten days. I now introduced with a 'heated' needle a little piece of the fungus, in the filamentous form, from the first glass of Pasteur's solution. This retained the filamentous mode of growth in the

[1] The actual time was much longer than I had intended, viz. two days. A subsequent experiment, in which one hour and twenty minutes was the period of immersion, was equally successful. Even after the two days of the present occasion, the carbolic acid did not seem to have affected the albumen, which was free from coagulation to the surface.

[2] This was a most troublesome procedure to carry out. I afterwards simplified the process very much, so as to dispense with both the spray and the filter, extracting the albumen with 'heated' pipette passed into a hole made in the carbolized shell with 'heated' forceps, a piece of carbolized cotton-wool being wrapped round the pipette and egg to prevent entrance of dust, filtration of the mixture of albumen and water being effected by decanting through a boiled syphon, which had a piece of sponge tied over the end in the flask.

new habitat, but increased so slowly that after the lapse of six weeks the little woolly mass which lay at the bottom of the glass had only grown to the height of an eighth of an inch, while the patch of scum was but very slightly larger than before, and a mere trace of granular deposit was seen upon the glass.

But though the growth of the organism in this medium had been so extremely languid, it had effected a very remarkable change in its constitution, the liquid, though still clear, having been altered from its original crystal purity to a deep rich brown colour, like that of porter.

It happened that I had inoculated another glass of this same albuminous fluid seven weeks previously with another very delicate filamentous fungus, which I must not here describe. The species had developed very luxuriantly, so as to occupy the greater part of the liquid with its white woolly growth, and clamber some distance up the inside of the glass above. Yet the colour of the fluid was scarcely altered at all, having a barely perceptible pale brownish tinge, and this circumstance made the great effect of the scanty growth of the *Oidium Toruloides* the more striking. At the same time, the dark brown liquid was entirely destitute of odour, and thus I obtained for the first time demonstration of what I have long suspected, as the result of experience in antiseptic surgery, viz. that an albuminous fluid may be affected with a fermentative change without the occurrence of smell. I have seen, for example, a psoas abscess furnish merely a slight oozing of serous discharge under antiseptic management, till a single careless application of the dressing admitted, as I believed, some fermentative organism, which, without giving rise to any odour, so altered the character of the discharge, as to stimulate the diseased part to profuse suppuration, leading to death by hectic. I have also observed erysipelas occur in spite of antiseptic treatment, and occasion profuse suppuration without smell, although from analogy there is reason to suspect that the virus of that disorder is of the nature of an organism, operating as a ferment upon the animal fluids. Facts such as these had often led me to express the view which at the time might be regarded as transcendental, but which the above observation proved to be a truth.

Thus this single insignificant species, when subjected to the precise method of investigation which I have described, afforded proof of several important general truths, which may thus be recapitulated.

1. It shows how greatly such organisms may vary under the modifying influence of different media.

2. It affords another clear example of the origin of a torula from a filamentous fungus.

3. It shows that the corpuscular form of such an organism may differ in fermentative energy from its filamentous parent.

4. That the corpuscular habit of growth acquired in one medium may be retained for a considerable time after the organism has been restored to a habitat in which the corpuscular form did not originally present itself.

5. That when placed in a more favourable medium, the toruloid variety may reproduce the purely filamentous.

6. This plant is another instance of an organism which is not bacteric, giving rise to a putrefactive fermentation in urine.

7. It proves that an albuminous liquid may be affected with a fermentation with inodorous products.

Lastly, The trustworthiness of the method of investigation is strikingly confirmed by the fact, that in none of the glasses of Pasteur's solution, urine, or albuminous fluid inoculated with this oidium, and in neither of the glass gardens, did bacteria, or any other kind of fungus besides the one intentionally introduced, make their appearance during the entire month in which the observations were made.

EXPLANATION OF PLATES VI TO X

Plate VI

Fig. 1, a pencil of fructifying threads of the common blue mould *Penicillium Glaucum.*

Fig. 2, a group of cells of the yeast plant, *Torula Cerevisiae.*

Fig. 3, Bacteria from various sources. The pair below the letter *a* are examples of a granular appearance of the protoplasm, and the presence of a distinct nucleus in each segment. *b* a Leptothrix filament, some of the segments being nucleated.

Fig. 4 illustrates the ordinary mode of growth of Bacteria, viz. by increase of the segments lengthwise and transverse segmentation. When first sketched, at 7.30 a.m., the object consisted of three segments, a_1, c_1, b_1. During the few minutes that elapsed between the completion of this sketch, and that at 7.42 a.m., the uppermost segment b_1 is seen to have increased in length to the size shown at b_2, and the two lower ones are not only longer, but each presents a transverse line of segmentation, while the middle segment is bent at this new place of division, c_2. Three minutes later the three lowest of the five segments of which the object now consisted separated from the other two, and in the sketch taken at 7.48 they are shown thus detached, the lower two obviously increased in length. Two minutes later one of these three was found to have separated and moved off, and the remaining pair were observed to swim away as an ordinary double bacterium.

Fig. 5 represents a minute organism, consisting of granules grouped in a different manner from that which commonly prevails among Bacteria. The difference of arrangement is explained by difference in the mode of growth, as is illustrated by the sketches c_1, c_2, c_3, and c_4, which represent the same granules in process of fissiparous generation. It will be observed that the granules, instead of increasing like ordinary Bacteria in one direction only, swell up in all dimensions and afterwards undergo segmentation, either into pairs or into fours, as indicated in the letterpress, p. 281.

Fig. 6 represents a form of Torula which resulted from the mingling of a drop of rain with fresh uncontaminated urine. Appearing in the first instance as an unmixed Torula (a), it changed in course of time to a delicate filamentous fungus (b and c) bearing buds, some of which were more or less toruloid in aspect and habit of growth, while others were morphologically identical with Bacteria, as described in detail in the text.

Plate VII

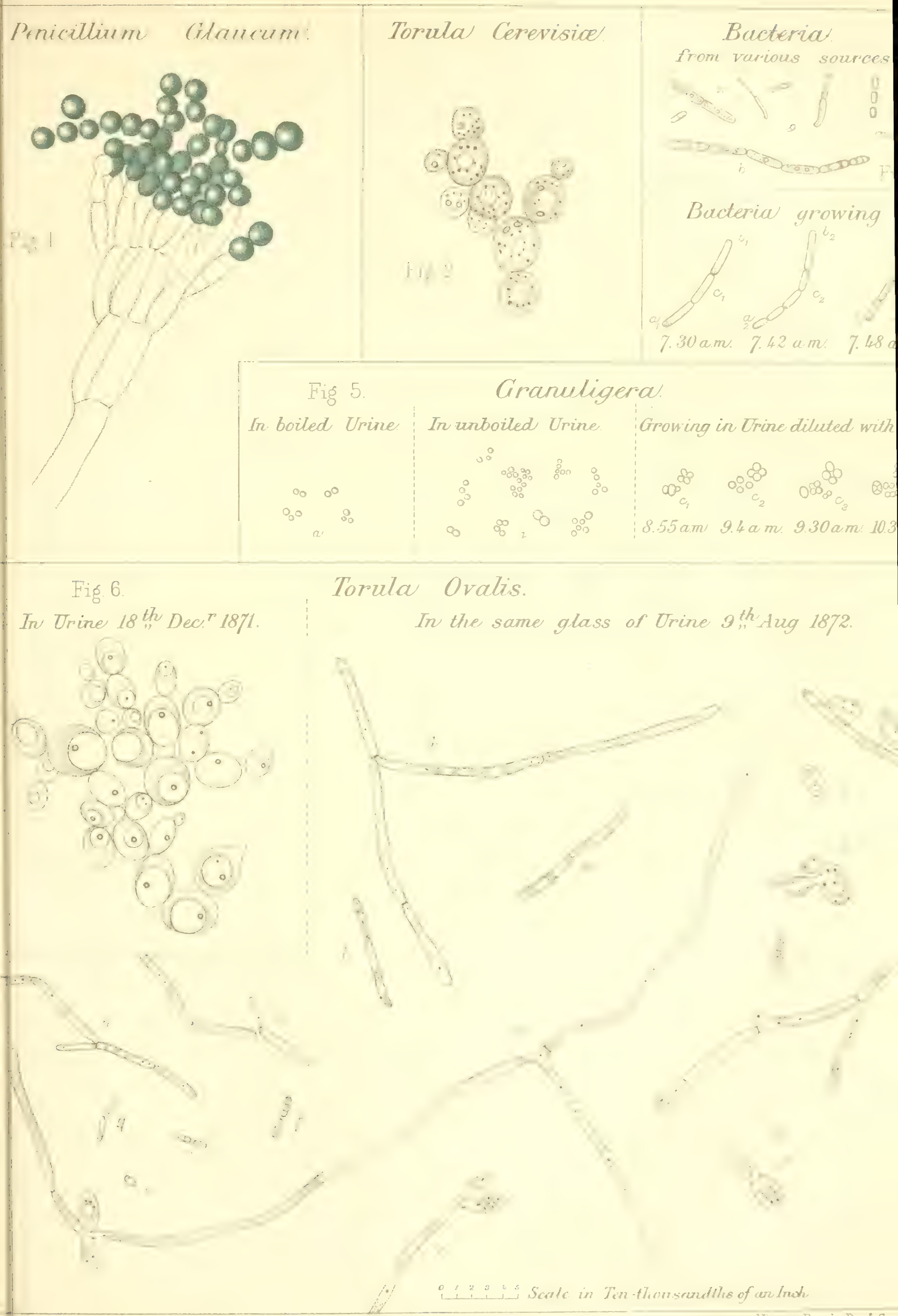
represents the same organism (*Torula Ovalis*), varying in character according to the medium in which it grows, and the period during which it has inhabited it. For a detailed description, see letterpress.

Plates VIII, IX, and X

show a minute fungus varying according to its habitat, from a filamentous growth to Torulae of very different characters, all distinctly traced to one and the same organism. For a detailed description, see letterpress.

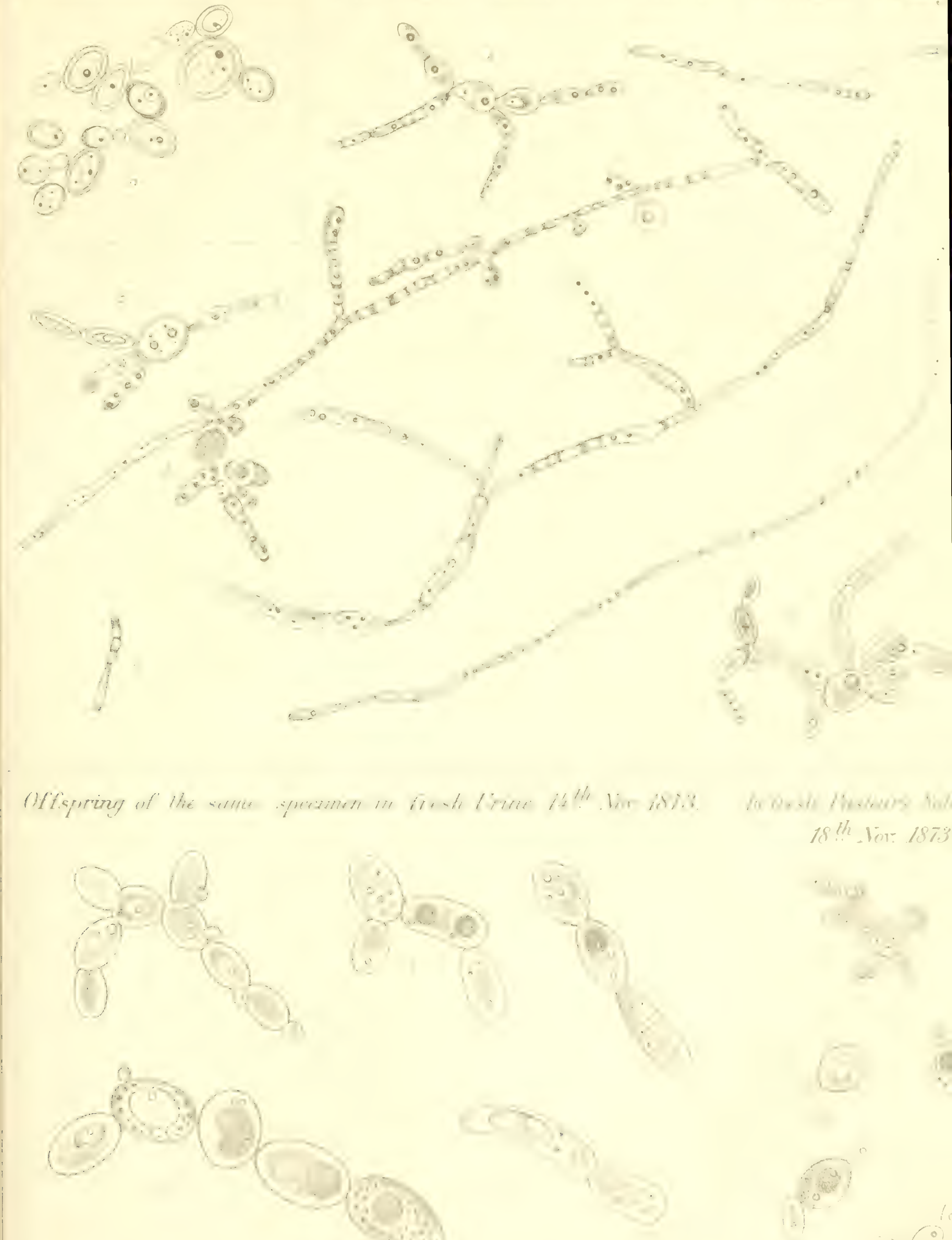
These illustrations are all taken from camera-lucida sketches, the magnifying power being 1,140 diameters, except in some cases where it is lower, as indicated by the scales on the plates.

Plate VI



delt. Vincent Brooks Day & Son

Torula Ovalis continued



0 1 2 3 4 5 Scale in Ten thousandths of an Inch

J. Lister del.

Vincent Brooks Day

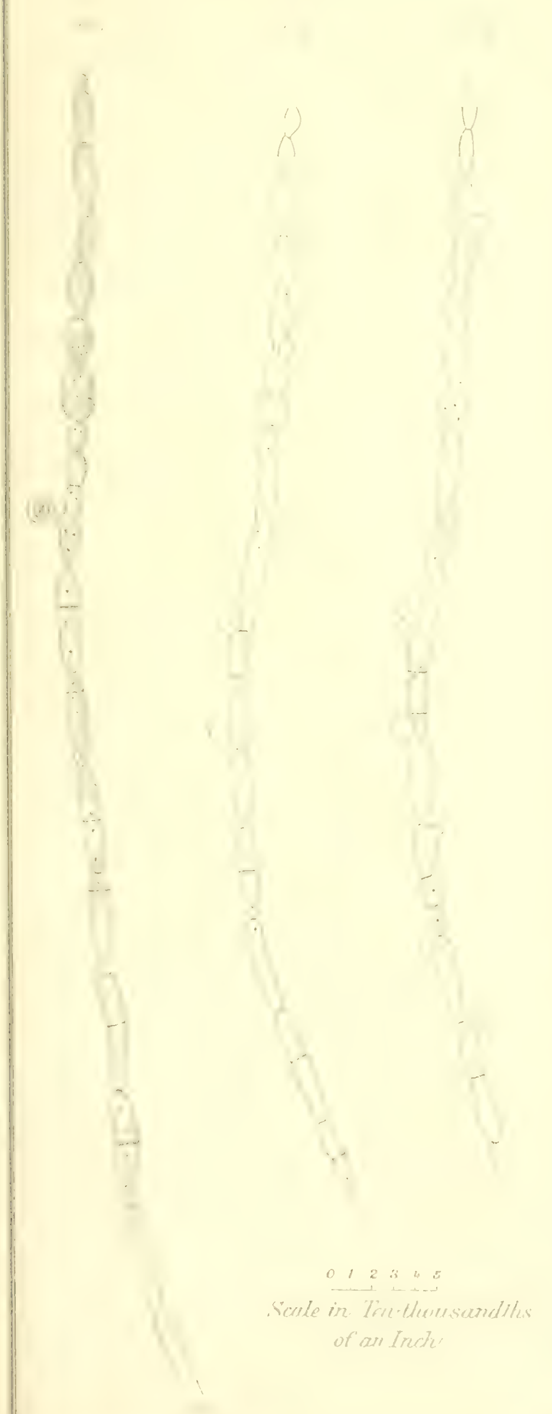
Oidium Toruloides

Fructifying Filament

from a glass of stale Pasteur's Solution examined in Water.

15th Aug. — *16th Aug.*

7. 25 p.m. — *11. 45 a.m.* — *1. 45 p.m.*



In fresh Pasteur's Solution, Glass No.

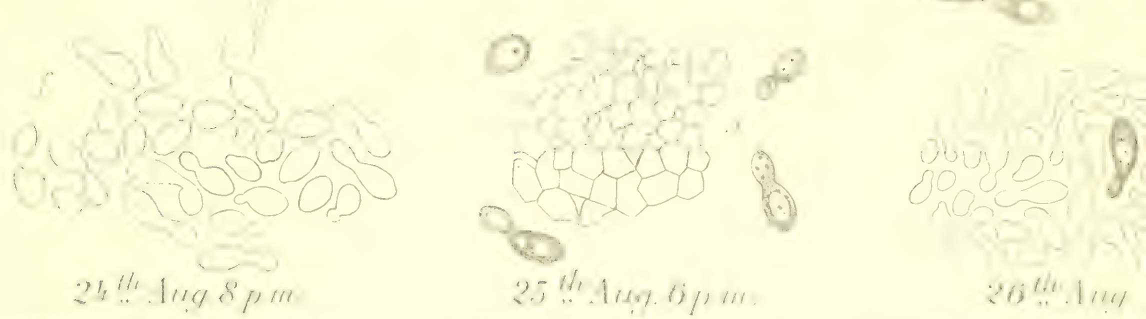
In fresh Pasteur's Solution, Glass No. 2.

0 1 2 3 4 5
Scale in Ten-thousandths of an Inch

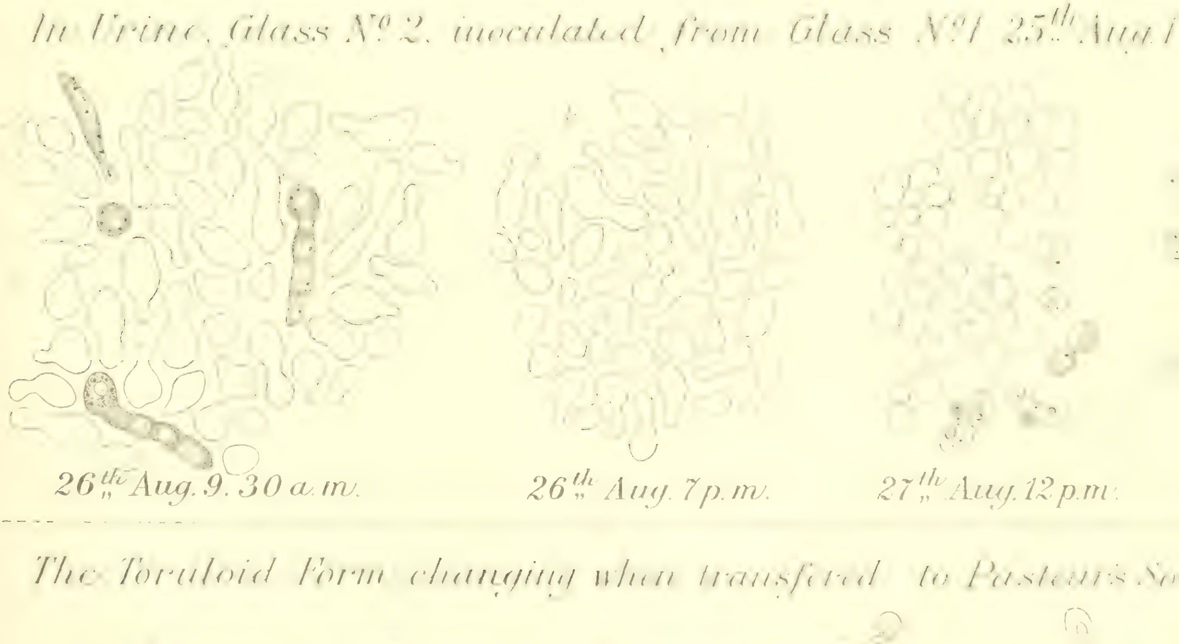
0 1 2 3
Thousandths of an Inch

Oidium Toruloides continued.

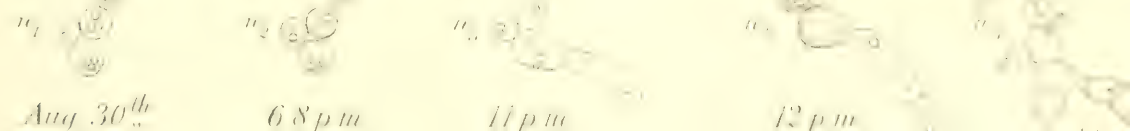
In Urine, Glass No. 1 inoculated 21st Aug.



In Urine, Glass No. 2. inoculated from Glass No. 1 25th Aug.

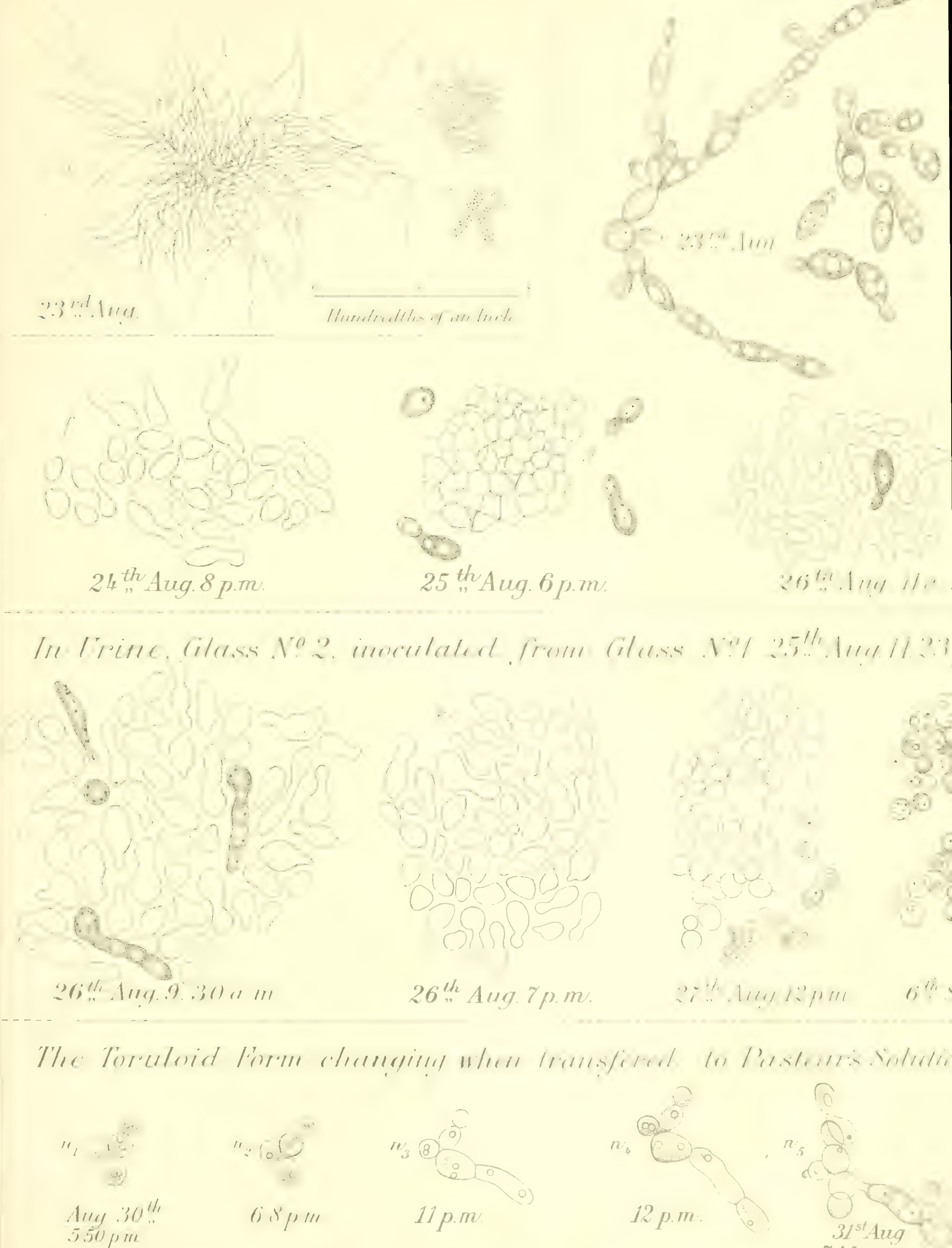


The Toruloid Form changing when transfered to Pasteur's So



Oidium Toruloides continued

In Urine, Glass No. 1 inoculated 21st Aug.



A FURTHER CONTRIBUTION TO THE NATURAL HISTORY OF BACTERIA AND THE GERM THEORY OF FERMENTATIVE CHANGES

[*Quarterly Journal of Microscopical Science*, October 1873.]

In April of this year I communicated to the Royal Society of Edinburgh some of the results of a protracted investigation into various circumstances connected with the appearance and growth of minute organisms in fermentable substances.[1] During the time that has since elapsed I have continued to prosecute the inquiry, and have obtained various new and striking confirmatory facts, a selection from which will form the subject of the present paper.

In the former communication observations were related which led me to conclude that in some minute species of hyphomycetous fungi, the spores (conidia) produced upon their filamentous branches germinate in three distinct ways; first, they may form comparatively thick sprouts, which become young plants, like the parent; second, they may multiply by pullulation like the yeast plant, and under some circumstances this toruloid growth[2] may continue for an indefinite period, though the resulting progeny will, under favouring conditions, reproduce a fungus like the original; and, thirdly, the conidia may shoot out sprouts of exquisite delicacy which break up into bacteria. In accordance with this mode of origin of bacteria it was shown that such organisms, like the fungi from which they are derived, are of various totally distinct kinds, manifesting their differences both morphologically and still more physiologically by the characters of the fermentative changes to which they give rise, and by the circumstance that some sorts refuse to grow at all in media in which others thrive. Some of the species exhibited most remarkable variations in size, form, and movement when introduced into different media, and sometimes gave indications of their fungoid origin by indubitable branching, and, in the thicker forms, by the presence of nuclei or vacuoles. Yet, however much any such modification might differ from the form in which the species was seen in another medium, the latter variety could be reproduced at pleasure by reintroduction into the habitat in which it was originally seen.

Hence any classification of bacteria hitherto made, from that of Ehrenberg

[1] Printed at page 275 of this volume.

[2] Considering the differences among authors in the use of the term torula, it seems justifiable for the sake of convenience to retain the old sense, as applicable to organisms like the yeast plant.

to that of Cohn,[1] based upon absolute morphological characters, is entirely untrustworthy. In order to determine the species of any particular specimen it is necessary to take into account not merely its appearance, but also the character of the medium in which it occurs. Even then mere morphology will often entirely fail us unless we are able to ascertain the physiological characters. And even these appear by no means constant ; for we shall in the present paper see reason to believe that one and the same bacterium may differ at different times in its fermentative effects on one and the same organic solution.

It is obvious that to trace the modifications of any one such organism through a series of successive habitats would be an utter impossibility if bacteria or any kind of fungi were liable to be evolved from the mere chemical constituents of the liquids employed ; and thus the investigation, though not undertaken for the purpose of combating the doctrine of spontaneous generation, has afforded the strongest possible evidence against it, and in favour of the germ theory of fermentative changes. For even in organic liquids such as milk, in which spontaneous generation has been said to be most liable to occur, it required only a rigorous attention to experimental details to ensure the complete absence of either organic development or fermentative change, except where organisms were intentionally introduced. But when this was done, the particular species used for inoculation grew unmixed with others, attended by the chemical alterations characteristic of it.

In order to enable the reader to give credence to my statements, it is essential that I should describe in detail the mode of procedure in its most improved form. Let us take, as an example, the case of boiled milk. The first thing to be done is to ensure that the interior of the vessel in which the liquid is to be heated shall be free from any living organisms. This is done by subjecting a Florence flask to a very high temperature, after providing that the air which enters on cooling shall be effectually filtered of living dust by passing through asbestos which, I find, answers this purpose quite satisfactorily. The asbestos is placed, in a mass about a quarter of an inch thick, between two layers of tinfoil sufficiently broad and long for wrapping round the junction of the neck of the flask and a glass cap that covers its mouth ; and when it has been so arranged, fine iron wire is tied tightly round, so as to compress it firmly as well as retain it in position after the outer layer of tinfoil has been dissipated by

[1] It is, however, only just to Professor Cohn to state that he dwells largely upon the different physiological effects of different supposed species of bacteria, and sometimes makes them a ground of classification, more especially in the group of ' pigment bacteria ', which he distinguishes from others on account of the remarkable colouring matters to which they give rise. Nevertheless he relies in the main on absolute morphological characters. See ' Untersuchungen über Bacterien ', von Dr. Ferdinand Cohn. *Beiträge zur Biologie der Pflanzen*, Zweites Heft, Breslau, 1872.

fusion and oxidation. The flask, previously mounted in strong wire for convenience of holding with forceps and for suspension, is then roasted thoroughly over a large Bunsen's burner and hung up by its wire mounting to cool.

The next point is to introduce the milk without contaminating any part of the flask except the lower portion that receives the liquid. For this purpose a funnel is used sufficiently long to reach from some distance above the mouth of the flask to its bottom ; and the exterior of the tubular part of the funnel is freed from living organisms by wiping it with a cloth, soaked in a strong watery solution of carbolic acid (one part of the acid to twenty of water), and drying it with a carbolized rag prepared by immersing it in a solution of one part of the acid in a hundred parts of anhydrous sulphuric ether and allowing the ether to evaporate.

This is much more convenient than heating the thick glass of the funnel, as I did in my earlier experiments ; and I may add that throughout this investigation I have found great advantage from thus substituting the use of chemical antiseptic means for the employment of a high temperature when the former happens to be more convenient. And I may remark incidentally that the results have afforded most conclusive evidence of the efficiency of a strong watery solution of carbolic acid for destroying minute organisms ; for throughout the whole course of the experiments I have found cleansing with such a lotion exactly on a par in this respect with exposure to the gas flame.

The tube of the funnel, thus freed externally from living germs, is passed down to the bottom of the flask, the asbestos having been previously removed and the glass cap lifted after wiping its margin with carbolic lotion for the chance of any organism having been applied to it in the process, and a piece of carbolized rag being wrapped round the mouth of the flask and the funnel to exclude living dust, the milk is poured in so as to fill not more than the lower half of the body of the flask. The funnel is then withdrawn through the rag, scrupulous care being taken that its extremity, now contaminated with the milk, does not touch the side of the flask. A substantial piece of cotton-wool carbolized in the manner above described is then tied over the mouth of the flask to filter any air that may regurgitate during the next stage of the process, the heating of the milk. This is done by immersing the body of the flask in a saucepan of boiling water and retaining it there for about an hour, care being taken that the boiling water never sinks below the level of the milk. By this means we are sure that the milk has been throughout exposed to the temperature of 212° Fahr. for the period desired, while the earlier parts of the process give us equal assurance that the whole interior of the flask above the milk is free from living organisms. The immersion of the flask in a bath of boiling water, for which

I am indebted to a suggestion of Mr. Godlee, of University College, London, has three advantages over boiling by direct flame ; it avoids frothing, which in the case of milk is extremely troublesome, and also the sputtering to which Dr. Roberts, of Manchester, has drawn attention ;[1] it prevents any loss of water by evaporation, and so disposes of the vexatious question of whether the specific gravity of the liquid has not been so raised as to render it unfavourable for organic development ; and lastly, it avoids any ' burning ' of the milk with its accompanying chemical changes.

The milk having been allowed to cool completely, a portion of it is decanted off into experimental glasses. These are plain ' liqueur-glasses ', each provided with a glass cap shaped like a small evaporating dish (made to order at any glass work) and covered with a small glass shade standing on a square piece of plate-glass. The glass plate has the double advantage of allowing the glass to be removed without disturbing the glass shade, and also of preventing the air beneath the shade from acquiring an accidental odour such as is derived from wood or other porous substances, and interferes with judging of chemical changes by the sense of smell.

The glass shade and glass cap have in combination the effect of perfectly excluding all living dust, although, as neither cap nor shade is made to fit closely, a constant free interchange by diffusion between the air in the liqueur-glass and the gases of the atmosphere is permitted. Hence, provided always that the liqueur-glass and its cap are free from living organisms to begin with, and that the contained liquid is similarly circumstanced, the latter will remain for an indefinite period unchanged except by gradual loss from evaporation, till at length in the course of months it dries up into a solid mass.

Further I have found as a matter of experience that if the glass shade and cap are raised, in a part of the room free from draughts, for the purpose of inoculation of the liquid or withdrawal of a small quantity for examination, there is practically no risk of the accidental introduction of organisms, provided of course that the operations be nimbly executed and that any piece of apparatus introduced into the glass have been suitably purified. For it appears that organic germs are not nearly so abundant in the atmosphere as is sometimes assumed, and only a very small fraction of the portions of dust with which the air of an occupied room is loaded have such germs adhering to them. Thus, in one instance the sole result of exposure of a glass of uncontaminated urine for half an hour in my study was three plants of three different kinds of filamentous fungi, each growing from one point and enlarging thence in all directions, while the liquid remained otherwise unchanged in aspect, a fact which may

[1] See *Nature*, February 20, 1873.

probably be stated equally truly by saying that, of all the many particles of dust that fell in during that period, only three at most contained a germ capable of growing in urine.

Hence while it is most true that scrupulous care must be taken in these experiments, and that forgetfulness or slovenliness in their execution would be absolutely fatal to success, yet it is equally true that by the very simple means which I am now describing the observations may be made with a facility and precision that leave nothing to be desired.

The glass plate and shade are simply washed and dried with a towel, but the liqueur-glass and its cap must be purified by heat like the flask. This is very simply done by bringing both to a high temperature over two spirit-lamps or Bunsen's burners, the liqueur-glass being held in the hand by its foot and the cap in a pair of forceps ; and the cap having then been placed on the glass, a substantial piece of cotton-wool with a bit of muslin beneath it (neither carbolized) is placed on the cap and tied firmly with fine iron wire round the glass beneath. The heat of the glasses ensures the destruction of organisms in the part of the cotton, which acts as a perfect filter during cooling ; and though the muslin may be browned by the high temperature, no empyreumatic odour is occasioned in the glass nor any deposit on its sides.[1] The glasses having cooled, the wire ligature is cut and the cotton carefully removed, the muslin beneath serving the purpose of clearing off all portions of cotton at once, and the glass and cap are immediately placed on the glass plate beneath the shade.

A series of experimental glasses, say a dozen, having been thus prepared, it remains to charge them by decanting from the flask, and this is a matter which, at the risk of appearing tedious, I am compelled to describe in minute detail.

The process is effected by means of a syphon of glass tube with a calibre of about one-eighth of an inch, the shorter leg rather longer than the height of the flask, and the other leg four or five inches longer. I find the most convenient way of purifying the syphon is to boil it, and in order to adapt it for packing into a saucepan, the glass tube is interrupted at intervals of about four inches with pieces of caoutchouc tubing, the shorter leg having one such india-rubber hinge, and the longer leg two. They are tied firmly on the tube with fine wire, silver wire being used for the shorter leg, where iron must rust. In the longer leg one of the caoutchouc junctions serves the further important purpose of enabling the assistant to control the flow through the syphon by compressing the india-rubber between the finger and thumb. A fourth piece

[1] It is only in my more recent experiments that I have thus employed the cotton, but there can be no doubt that while it scarcely adds to the trouble of the process, it must materially increase its security.

of caoutchouc tubing is applied, without tying, to the end of the longer leg, for adapting a syringe. The syphon thus constructed is filled with water and boiled for half an hour, and while it is still in the hot water, one of the caoutchouc junctions of the longer leg is seized with catch forceps (previously heated) to prevent the syphon from emptying itself when taken out. The longer leg being now raised from the saucepan by aid of another pair of heated forceps, the syringe, which has been washed out with carbolic lotion, and the nozzle passed through the flame, is applied to the terminal caoutchouc adapter. The shorter leg is next raised, and at once slipped through a hole in the middle of a piece of carbolized cotton-wool, and then into the flask (whose cotton cap has been previously loosened, so as to be ready for removal), and the end of the leg being kept a little above the level of the liquid, to avoid mingling of the water in the syphon with it, the cotton is tied round the neck of the flask and the syphon. Then, as the syphon is intended to be left permanently adapted to the flask to serve for future decantings, it is needful to provide against the access of organisms to the moisture between the india-rubber junctions of the longer leg and the glass tube. For this purpose, the catch forceps being removed, carbolized cotton-wool is wrapped round each junction, and a piece of rag over this to enable it to resist wear, and tied securely round the glass tube above and below the caoutchouc. The syphon is now emptied of its water by means of the syringe, and the shorter leg being pushed down till its extremity is in the liquid, the syringe is again brought into operation till the syphon is seen to be full of milk. The assistant then compresses one of the caoutchouc junctions through its cotton investment, to prevent the milk flowing out when the syringe and its adapter are removed. This is done with fingers dipped in the carbolic lotion, and the apparatus is completed by slipping upon the glass tube that now terminates the syphon a circular piece of thin caoutchouc, about two inches in diameter, with a hole in the centre just large enough to admit the tube, so that it remains in position without further fixing. This caoutchouc plate is to serve as a screen to keep dust out of the glasses while they are being filled. To keep it level it is strengthened by a fine wire run through and through near its margin, and, to ensure freedom from living organisms, it is steeped for half an hour or so in the strong carbolic lotion ; after which, as caoutchouc has the property of imbibing carbolic acid into its substance, the screen when dried retains a sufficient quantity of it to ensure the destruction of organisms that may come in contact with it. The experimental glasses, which as yet are covered with their shades at as short a distance as possible from the syphon, are successively exposed and charged, each being brought close to the syphon before the glass cap is raised, and then at once placed with its margin in contact with the caoutchouc screen, while the end of the syphon extends into the glass. The assistant is now directed to relax his hold upon the caoutchouc junction above, when the milk at once flows into the glass, and when this is about two-thirds filled, the flow is again arrested by the assistant, the glass removed, the cap, held in the other hand of the operator, is reapplied, and the glass placed again under cover of the shade.

All the glasses having been charged, the caoutchouc screen is slipped off and a piece of carbolized cotton tied over the end of the syphon, which being raised to a higher level than the fluid in the flask the assistant finally relaxes his hold and the syphon empties itself into the flask, becoming occupied by air filtered by the cotton tied over the extremity. When at any future time another set of glasses are to be charged, all that is needful is to remove the cotton-wool from the end of the syphon, re-adapt the syringe by means of a caoutchouc adapter, steeped for a short time in carbolic lotion, and then proceed as before. In this way we avoid the great loss of time involved in providing a fresh syphon for every fresh decanting, as I did in the earlier experiments.

The other experimental fluids employed in the observations about to be related were Pasteur's solution, turnip infusion, an 'artificial milk', consisting of a solution of sugar of milk and white of egg in water, and urine.

In preparing the Pasteur's solution for this set of experiments I deviated from Pasteur's formula in two respects; viz. the proportion of the water and the source of the mineral salts. I doubled the quantity of water, so as to make the liquid, as I hoped, more favourable for the growth of some organisms, more especially after loss by protracted evaporation as occurs in my experiments, and tap water was employed instead of distilled, so as to afford greater variety of saline material. For the yeast ash, which every one who has tried must have found extremely troublesome to prepare, I substituted the same weight of ashes left after burning a large amount of loppings from various kinds of trees and shrubs; the liquid obtained by lixiviation being filtered, and a quantity used in proportion to the estimated weight of dissolved solids. It seemed to me that the salts obtained in this way would be more likely to afford suitable pabulum for the growth of different organisms than those derived from one particular species of fungus. Thus, my Pasteur's solution had the following composition:—

Water from the tap	5000 grains
Lump sugar	250 ,,
Tartrate of ammonia	50 ,,
Salts from wood ashes	5 ,,

It happened that the alkalinity of the ashes exactly counterbalanced the acidity of my specimen of tartrate of ammonia, so that I had a perfectly neutral solution to work with. The flask was prepared and the fluid introduced as above described for milk, but the boiling was done by the direct flame and was continued only ten minutes.

The turnip infusion was prepared by boiling peeled white turnips, in about enough water to cover them, till they were soft, reducing each to a mash with a little additional water, filtering, and keeping the filtrate at 212° Fahr, for half an hour, as in the case of the milk.

The 'artificial milk' required special preparation. A solution of 160 grains of milk-sugar in ten ounces of tap water, which is about the proportion in milk according to Miller's *Chemistry*, was subjected to the temperature of 212° Fahr. for an hour and a quarter in a flask prepared and arranged as for the milk. Next day, the fluid being of course cold, I added five drachms of the white of a raw egg, the shell of which had been treated twelve days before with one to twenty carbolic-acid solution for an hour and twenty minutes and then wrapped in carbolized cotton, a process which, I may remark, preserves eggs from putrefaction, apparently for an unlimited period, although the carbolic acid leaves the cotton in a few days, and that which was applied to the egg-shell does not penetrate sufficiently to produce any coagulation whatever of the albumen ; and I have lately eaten an egg which had been prepared in this manner more than three months before, and for the last fortnight had been kept at 100° Fahr. A large pipette having been purified by heat, and protected from the entrance of dust in cooling by means of carbolized cotton, a plug of which in the upper end served the further purpose of preventing the entrance of organisms into it from a syringe with which it was connected by means of a caoutchouc adapter, a small hole was made in the shell of the egg with carbolized fingers and heated knife, and the narrow end of the pipette being inserted between the yolk and the shell, and a piece of carbolized cotton wrapped round the pipette so as to cover the orifice and exclude dust, almost all the white was extracted without interfering with the yolk, and transferred at once to the sugar-of-milk solution in the flask, the cotton round the pipette serving as a temporary screen, for which a substantial cap of the same material was substituted on removal of the pipette. Twenty-four hours later, the flask having in the interval been occasionally agitated to diffuse the albumen, a syphon was introduced with the peculiarity that a piece of sponge was tied over the end of the shorter leg to serve as a filter for excluding the shreddy undissolved residue of the albumen, the sponge being of course purified by the boiling. The artificial milk was thus obtained with only trifling turbidity when decanted into experimental glasses, and the stock in the flask has remained unchanged to the present time (September 1873), more than three months after it was prepared.

The urine was not boiled at all, but was obtained altogether unaltered by a very simple process, depending upon what appears to be a fact of high interest both physiologically and pathologically, that a mucous canal in a state of health does not permit the growth of foreign organisms in its immediate vicinity, so that preliminary external application of a carbolic lotion (1 to 40) is sufficient to ensure an uncontaminated state of the fluid, which, with its unaltered mucus, is a much more favourable nidus for organic development than after boiling.

One other piece of apparatus requires a short notice, viz. that used for withdrawing fluid from the experimental glasses for inoculation or examination. The most convenient means for this purpose I have found to be what may be called a 'syringe pipette', consisting of a small syringe with a piece of glass tube connected with it by a caoutchouc adapter, the junction being self-supporting but yielding (as distinguished from rigid). This last property permits the use of a very delicate tube without risk of breakage when it touches the side of a glass; and it is of great importance that the tube should be of as *thin* glass as possible. It can then be heated fully when dry by once drawing it quickly through the flame of a Bunsen's burner, and a few seconds suffice for its cooling. The tube, which is about a line in diameter, is drawn out a little at the end, and is bent at an obtuse angle about two inches from the syringe; so that the latter is not held over the liquid during the process. Care is taken not to drive any air from the syringe into the tube after heating the latter, and rather more of the liquid than would suffice for inoculation is taken up, so that the part left in the tube may protect that which is ejected from air from the syringe.

To the general reader these details may seem almost unpardonably minute, but for any one who is desirous to repeat similar experiments I venture to hope they will not be found so.

On the 14th of June I drew off for the first time some milk from the flask which was exhibited to the Royal Society of Edinburgh in April as having its contents still fluid, and therefore probably unaltered, though prepared seven weeks previously, and under difficulties as compared with the material of later experiments, inasmuch as it was boiled by the direct flame of the lamp, the extreme inconvenience occasioned by the frothing of this flask having led to the suggestion of the boiling-water bath above described. Also the cotton-wool over the mouth was not carbolized, a piece of muslin between the cotton and the flask being alone treated with the ethereal solution of the acid. Nevertheless, the cotton filter had proved efficient in spite of the often repeated rapid rushing of air into the flask which must, of course, have occurred whenever the lamp was removed to prevent the froth from reaching the cotton. For the milk when decanted just four months after the boiling, proved perfectly good, having a slight flavour of turnip as might be expected of winter milk ; its reaction showed the peculiar character now known to be possessed by that fluid when fresh, purpling blue as well as red litmus paper, and the microscope showed no appearance of organisms or of the granular masses of deposited caseine often seen as an early indication of fermentative change, while the milk globules were bright and unaltered.

These observations were made upon the first two or three drachms that flowed from the syphon, received into an unprepared glass, as should always be done to wash out any residual water from the tube, and thus ensure uniformity of the contents of the experimental glasses. Of the latter, one was at once exposed in my study by removing the shade and glass cap to receive any organisms that might fall into it, and was covered again with cap and shade after fourteen hours, including the night and early morning in which the furniture was ' dusted ' with a cloth by the servant, but the glass carefully avoided. It was then placed beside the other glasses in a cupboard, the temperature of which varied from about 65° to 70° Fahr.

On the 20th of the month I observed for the first time a delicate filamentous fungus on one part of the side of the glass, extending upwards from the milk for about an eighth of an inch ; and at the same time a semitransparent layer which had been noticed for about two days previously at the surface of the milk was found to have increased in thickness. Two days later this layer had attained a depth of one-sixth of an inch, and I proceeded to investigate its nature, thinking it probable that it might be a change induced by the growth of the fungus. But on trying to take up a portion with the syringe pipette, I encountered a most unexpected difficulty in extreme viscidity of the liquid. I had before observed the effects produced upon milk by thirteen different organisms, including six distinct kinds of bacteria, but though the products had differed extraordinarily in colour, reaction, and consistence viscidity had in no case been witnessed. Here, however, the upper part of the milk had been converted into the most viscid substance I ever saw. When I at length succeeded in extracting the pipette without any of its contents getting upon the outside of the glass, I found that on touching any object with the delicate end of the tube and withdrawing it, the tiny drop became extended into a thread a foot and a quarter in length, as delicate as the finest spider's web and barely visible from its tenuity. I afterwards amused myself with spinning webs from one object to another. When dry they exhibited considerable tenacity, and thicker ones broke with an audible snap when subjected to longitudinal traction, while the finer ones floated like gossamer in the air. Here, then, was an amazing chemical change effected in the milk, and one of great interest with reference to the elaboration of mucus and other viscid secretions in the animal economy. On applying the microscope I found no fungus filaments, but multitudes of motionless bacteria, such as are represented in Plate XI *m*, very minute and delicate, and often showing a peculiarity only badly represented in the specimens drawn, viz. that of having one part of the organism of much higher refractive power than the rest. In the lower part of the glass similar bacteria were seen in active movement, often curiously wriggling and sometimes rotating completely round a transverse axis. The reaction of the milk was also changed, distinctly reddening blue litmus paper and not affecting red.

Next day I introduced into another of the glasses of milk a morsel of the viscid substance by means of a pair of mounted needles passed through the flame. A glass of the artificial milk above described, which had been decanted for seventeen days and had undergone no change, and a glass from a flask of Pasteur's solution which had been prepared on the 11th of February, and remained brilliantly clear, were also similarly inoculated.

In the course of two days observing a translucent layer, about a line in thickness, at the top of the milk in the second glass, I removed some for examination. It was distinctly acid in reaction but uncoagulated, and when a drop was diffused on a glass plate the liquid was seen to be generally thin and turbid, but studded with transparent specks which, when touched with the point of a needle, could be drawn out into threads like the viscid material of the first glass. On applying the microscope to one of the transparent specks, multitudes of motionless bacteria were seen, such as are represented at *o*, Plate XI, showing in a striking manner the peculiarity before described, of having their extremities of different refractive power from the rest. The thin turbid part, on the other hand, was a finely granular fluid in which similar bacteria were seen in much smaller numbers, some of them moving freely, while others were motionless, the latter being each surrounded with a transparent halo of greater or less extent as is shown at *p* and *q*, Plate XI, and in some cases, the transparent areas surrounding different bacteria were confluent. These were evidently miniatures of the transparent specks visible to the naked eye; and they seem to me beautiful examples of a change effected by bacteria in the surrounding medium, whether due to vital action of the organism or to some substance (a so-called chemical ferment) emitted from it during life or after death.

The moving bacteria, it is to be remarked, had no transparent area around them, nor were they able to penetrate those that surrounded the motionless ones, proving the substantial character of the latter.

The artificial milk and Pasteur's solution were turbid the day after inoculation: and in the former, which I examined microscopically, were seen active bacteria of extreme minuteness, looking like mere pairs of granules, which on the following day had given place to others of larger size and of the same sort of characters as those of the milk, as shown at *n*, Plate XI. Similar bacteria were also seen at this time in the Pasteur's solution. But neither then nor at any subsequent period was there any viscidity of the general liquid in either of these glasses, implying that the viscid substance was no essential appendage of the organism, but the result of its fermentative action upon particular materials.

It is, however, to be added that in the course of the next month a deposit occurred upon the sides of both these glasses such as I never saw under any other circumstances, constituting a film which, in the artificial milk, resembled coagulated fibrine in its toughness, and in the Pasteur's solution was tenacious though not viscid, as if the motionless bacteria which constituted the deposit in each case had been glued together by a minute quantity of some intervening substance.

The next observation which I have to record has reference to the origin of bacteria. It will be remembered that a filamentous fungus made its appearance on the interior of the first milk-glass six days after its exposure. The growth continued to spread, and by the tenth day, as it had a bloom indicating probable fructification, I scraped off a small portion from the glass by means of a tenotomy knife washed with strong carbolic solution and dried in the flame, and examined the specimen in a drop of water with the microscope. It proved to be a fungus of great beauty composed of very delicate branching filaments (*a*, Plate XI), bearing spores (conidia) often septate, characterized by a raw sienna tint (*c*, Plate XI) which was often distinctly seen to be confined to an external envelope, affording, what is unusual with fungi of such minuteness, the means of definite recognition, and of ascertaining with precision the three modes of germination above alluded to (see pp. 302, 309). Many of the spores were seen to have produced thick sprouts to form young plants. Of these *d* has been sketched because it happened that, while part of the brown envelope had been consumed in the process of germination, a portion still remained for identification. Other spores were observed in toruloid pullulation, as is seen at *e* in a mass still connected with the parent filament, and at *g* in a free and septate spore, while *f* was either a spore multiplying by pullulation, or a young plant of a brown colour. For here and there young plants were seen like *b* retaining the brown investment of the spores; and hence, as a dark-coloured coat of threads and spores is the special character of the order Dematiei among hyphomycetous fungi, and as de Bary has given the name *Dematium pullulans* to a closely allied microscopic fungus,[1] I have ventured to suggest for this species the name *Dematium fuscisporum*. Further, the spores were often seen to give off exquisitely delicate threads as at *i* and *k*, while in *h* we have a combination of this delicate sprouting with toruloid pullulation in the same spore. Finally, there were observed in abundance among the filaments free bodies like *l* exactly resembling in form, size, and refractive power portions of these delicate sprouts. Some of them, not sketched, were seen to be branched, and yet, though in this respect and in the absence of the double rod-like character they deviated from the most typical form of bacteria, their bacteric nature was rendered indubitable by characteristic movement observed in several instances. I may add that in *k* that which is sketched as a branch of the delicate sprout was seen to oscillate from the position indicated to that of the dotted line, as if about to detach itself; though this is an observation to which I do not wish to attach much importance, as the same appearance might possibly result from an accidental adhesion of a previously free bacterium. Taking the observation as a whole it affords proof positive of three distinct modes of germination of the spores of one and the same fungus, while there seems little reasonable doubt that the third mode was the source of the bacteria.

It will be remarked that the bacterium which grew thus abundantly among the filaments of the *Dematium* on the dry glass differs entirely in appearance from that which was found in the milk and produced (as I think we are justified in saying) the viscous fermentation. And there is reason to think that they were in reality two entirely different species, and that the one derived, as it appears, from the *Dematium* (or some other exactly like it morphologically) which I have indicated in the plate as *Bacterium No. II*, existed in the milk along with that of the viscous fermentation (*Bacterium No. I*), though the latter took the precedence in development, so that the former escaped notice in the first instance; as so commonly happens when germs of different kinds are introduced together into the same medium. For having inoculated a glass of fresh urine on the 30th of July with a portion of the viscid material from the second milk-glass, the product which first showed itself five days later by dimness of the liquid had none of the characters of *Bacterium No. I*, but resembled in elongated and curved form as well as in dimensions the one derived from the *Dematium*, see Plate XI, *Urine, August* 4. It was of course conceivable that the appearances in question might be merely the result of a modification of *Bacterium No. I* by the new medium in which it grew; the other alternative being that two bacteria had existed together in the milk, but that *Bacterium*

[1] See *Morphologie und Physiologie der Pilze*, &c. Von Dr. A. de Bary, Leipzig, 1866, p. 183.

No. I was either incapable of growing in urine or had lost its vitality during the five weeks which had elapsed since its introduction, while *Bacterium No. II* had survived. The last appears to have been the fact ; for on inoculating milk and Pasteur's solution with the new bacterium, while it throve in both it retained the characters that it had in the urine and occasioned no viscidity of the milk. And further, when introduced into artificial milk, in which *Bacterium No. I* grew so rapidly, *Bacterium No. II* failed to grow at all, the fluid remaining unchanged for the twenty-six days during which it was kept under observation.

Some other points were observed regarding *Bacterium No. II* which appear of sufficient interest to be placed on record. When first seen in the urine it was unbranched, and exhibited rotatory movements ; but when again observed two days later it was found of larger size, and often distinctly branched, see Plate XI, *Urine, August* 6, and entirely destitute of motion. On this day a minute drop of the urine containing the organism in this condition was introduced into a glass of turnip infusion decanted from a stock of that liquid which was prepared on the 24th of February, and had then furnished the supply for twelve experimental glasses, but which retained its original characters as regards aspect, fresh odour, and faintly acid reaction, while the microscope revealed no organisms. After two days bacteria made their appearance of the characters shown in Plate XI, *August* 8, resembling those first seen in the urine in being unbranched, and even more active than they, with wriggling onward movement. Two days later the bacteria were again motionless and of larger size, and often manifestly branched, see Plate XI, *August* 10, the turnip infusion having now acquired a smell like that of strong turnip soup. Again four days later, the glass shade having lost all smell, I supposed the fermentation to be over ; but on examining a drop I was surprised to find that bacteria were present in abundance, but that all the large and branched ones had disappeared, and in their place was a progeny more minute than any seen before, showing sometimes the double rod form most characteristic of bacteria, see Plate XI, *August* 14, and exhibiting active movements of rotation and wriggling. The only explanation that suggested itself to my mind was that some material of limited amount in the turnip infusion yielded under the fermenting influence of the bacteria a volatile product (the same, perhaps, that caused the soupy smell) which, while it remained, exercised a modifying influence upon the organism, resulting in the branched and motionless variety, but on escaping, as indicated by the odourless state of the fluid, left the bacteria to return to their former shape and active movements. And this view was confirmed by the result of inoculating a second glass of the turnip infusion from the first on the 14th of August, when the bacterium had the minute and active state for the second time. For precisely the same series of changes of the organism was then repeated, as is sufficiently shown by the sketches, Plate XI, *August* 15, 18, and 20. I dwell upon these circumstances because they afford an example of modification of bacteria under different conditions of the same medium, and also an instance of branching, which has been spoken of by Cohn in his recent work as something altogether foreign to this class of organisms.[1] I also venture to hope that facts like these will tend to give the reader additional confidence in the trustworthiness of the mode of investigation.

One other circumstance with regard to *Bacterium No. II* seems deserving of mention. As already stated, when introduced into a glass of boiled milk, it grew rapidly, having after three days the appearances shown in Plate XI, *Milk, August* 18, with active movement. There was, however, up to this time no change in the aspect, odour, or reaction of the milk. But in the course of a few days the upper part of the liquid assumed a peculiar golden-yellow tint, and a fortnight after inoculation the appearance was almost as if the yolk of a bantam's egg were floating on the surface, while there was also some similar yellow material deposited at the bottom of the glass, and the main body of the milk had assumed a cream colour. The reaction was now distinctly though not strongly acid, but the glass shade had no sour smell, a very faintly urinous odour being the only one perceptible. The main body of the milk was a very soft coagulum, but the upper part was a thin, transparent liquid, the bright yellow material being deposited at the junction of the two. On examining a portion of the yellow substance with the microscope, I could discover nothing but a mass of motionless but unbranched bacteria such as are shown in Plate XI, *September* 1, and I could only conclude that the bacteria were themselves of yellow tint though too minute to show it under the microscope Yet it is a curious circumstance that the same bacterium in Pasteur's solution had not this colour, but produced a pale pink tint by the deposit which it formed at the bottom of the glass. At this period I was obliged to suspend my observations, but from what had been seen in the last few days it appeared that the bacteria were converting the coagulum into a transparent liquid, for the upper translucent layer was daily increasing in thickness. On looking at this time at the second milk-glass, in which the viscous fermentation had occurred at an earlier period, I found that the viscid upper part had changed to a similar golden-yellow colour, and under the microscope I found that *Bacterium No. I* had disappeared, and given place to *Bacterium No. II*. This yellow colour in milk I never saw caused by any other organism.

The last observations which I have now to relate refer to the commonest

[1] Op. cit., p. 130.

of all the fermentative changes to which milk is liable, that which results in the rapid evolution of lactic acid, and consequent precipitation of the caseine in the form of curd, a change which was attributed by Pasteur, so early as 1857, to the operation of a special organism.[1] The frequency of this change in milk does not, however, appear to depend on specially extensive dissemination of the ferment, but rather upon the circumstance that the organism which we are about to study, when it does gain access to milk, takes the precedence of others in development, and that dairies being places in which this particular ferment abounds, the milk supplied from them is sure to contain it, as they are at present managed. For it is a remarkable fact, and one well worthy of the consideration of the dairyman, that while milk supplied for domestic use will turn sour in summer weather within twenty-four hours, yet of all the many instances in which I have observed alterations in milk caused by organisms introduced through atmospheric exposure, in no single case did the true lactic-acid fermentation occur. Some organisms have given rise to a primary alkaline alteration, strong or feeble, some have been neutral in their effects, while others have produced an acid condition indeed, but only feeble and slowly developed.

It seemed worth while before closing this investigation, in which fermentative changes in milk had occupied a prominent position, to apply our method of inquiry to the most frequent and therefore the most interesting of them all. Accordingly on the 14th of last month, August, I obtained from a dairy near Edinburgh, pervaded with the usual sour smell, about a pint of milk said to have been taken from the cow four hours previously and tasting perfectly fresh, the dairy woman bailing it out with a tin vessel from the pan in which it stood into a clean glass bottle which I had provided. One hour later about ten ounces were introduced into a flask purified by heat, and were subjected to the temperature of 212° Fahr. for three-quarters of an hour, the arrangements being such as have been fully described above, see p. 310, and on the following day four experimental glasses were charged each with about half an ounce of the milk by means of a permanent syphon (see above). The first milk that came from the syphon, received into another glass, had the taste of perfectly fresh boiled milk, it purpled both blue and red litmus paper, and exhibited under the microscope nothing but milk globules of all sizes including extreme minuteness. Meanwhile, the milk remaining in the bottle had undergone the usual change. At noon, twenty-three hours after it was taken from the cow, it tasted distinctly sour though still fluid, and sharply reddened blue litmus, and on microscopic examination motionless bacteria were seen in considerable numbers, of soft or

[1] 'Mémoire sur la Fermentation appelée Lactique,' *Annales de Chimie et de Physique*, 3me série, tome lii, 1858.

delicate character, in pairs, fours, and chains (*leptothrix* filaments) as represented at *a* in Plate XII. The milk examined was in a wine-glass into which it had been poured from the bottle, and this was kept covered till 5 p.m. when a small drop was taken out for inoculation of one of the glasses which we may term *Boiled Milk I*. It was now more sour to the taste, and more sharply acid to litmus, and when diffused between plates of glass exhibited small white masses which the microscope showed to be granular (deposited caseine) while the motionless bacteria before observed were again seen in abundance. The glass also contained some larger portions of soft curd. Next day at 8.30 a.m., or fifteen and a half hours after inoculation, *Boiled Milk I*, though unaltered in appearance, had communicated a faintly sour smell to the air under the glass shade, while the smell of boiled milk was gone. A drop removed by pipette reddened litmus more than on the previous day, though still faintly blueing red paper, and under the microscope motionless bacteria were seen in considerable numbers exactly similar to those observed in the unboiled milk, except that there was greater variety in their size, some being considerably larger, as shown in the plate at *b*. At 5 p.m., twenty-four hours after inoculation, the glass shade gave a pleasant smell of slightly sour milk, and the reaction was sharply acid, but the milk was still fluid, and next morning rather more than thirty hours after inoculation the milk had set into a solid mass.

On the same day (August 15) that *Boiled Milk I* was inoculated as above mentioned, parallel experiments were made with turnip infusion and with urine, each of which received a minute drop from the same glass of sour milk. The turnip infusion was from the stock prepared in February, having both naked-eye and microscopic appearances unchanged ; and the urine was a glass prepared at the same time as that used for *Bacterium No. II*, retaining unimpaired in every respect the characters which it then had, seventeen days before. Neither of these glasses showed any signs of bacteric development on the 16th, the day after inoculation, but on the following day both were manifestly nebulous, and both exhibited under the microscope numerous motionless bacteria. There was, however, a remarkable difference between the organisms in these two glasses. In the turnip infusion the bacteria did not differ very greatly from those in the boiled milk, except that the leptothrix form was very seldom seen, and that the segments of the pairs were sometimes of greater length, while unjointed specimens, also pretty long, made their appearance, as at *c*. In the urine on the other hand the deviations from the form in the milk were most remarkable, as will be sufficiently evident from an inspection of the plate under *Urine I*. Some indeed, like *d*, were not very different from the original leptothrix form, but even such specimens often exhibited, as that one does, an elongated state of some of the segments of the chain, thus forming connecting links between the leptothrix and the widely different spirillum-like specimens such as *e*. Next day the same sort of appearances were again seen, and an observation made on the previous day was confirmed, viz. that vacuoles were present in the thicker specimens. This is well shown in the sketches *g* and *h*, in all of which there is also a further deviation from the type which has been lately held to be invariable in the entire group of bacteric organisms, and from whence the name schizomycetous, as applicable to a totally distinct order of fungi, has been derived, that is to say these bacteria, instead of multiplying by transverse fission, are plainly increasing by pullulation, that is to say, by shooting out buds after the fashion of the yeast plant ; and it will be observed that these sprouts are by no means always in a line with the long axis of the organism from which they spring. Yet that they really were the same bacterium was evident, not merely from transitional forms, but from specimens such as *f*, in which in one and the same chain we have the leptothrix character combined with the long and thick vacuoled and pullulating organism. Similar observations were made on the following day ; and now even the smallest and most bacteriform specimens sometimes exhibited a minute vacuole, as is shown at *i*. These appearances did not startle me as much as they would have done had I not seen something almost exactly similar in an earlier part of the investigation, though in another species of bacterium under totally different circumstances.

Thinking it worth while to try how this organism would behave if transferred from the urine to Pasteur's solution, I used for that purpose some of the old February stock, still perfectly bright, inoculating on the 18th. Next day the fluid was distinctly nebulous as examined before a candle, and under the microscope I found motionless bacteria, not numerous, but obviously of new formation from the delicacy of their aspect, represented at *k*, in Plate XII, where they are seen to be of considerable thickness and length of the segments, which present a curious alternation of lightness and darkness in their substance. Though a pair and three are given in the sketch as well as a single one, solitary individuals were much the most frequent. Such was the appearance twelve hours after inoculation, but when twelve more hours had expired a very great change had taken place. Not only were the bacteria much more numerous, but very much smaller ; and instead of being commonly single, were invariably double, having in fact the ordinary appearance of minute bacteria (see Plate XII, *l*), and to complete the metamorphosis some of these bacteria were seen swimming actively in ordinary bacteric fashion. Two days later the liquid was considerably increased in opacity and I was struck with what I had never seen before in Pasteur's solution, a sort of dirty or dingy appearance, as if a very small quantity of ink had been mingled with the liquid, and the deposit at the bottom of the glass, which was white on the previous day, had now the same dingy cast. Under the microscope the bacteria appeared much as on the last occasion, except that some were even more minute than any then were, so that it was impossible to say, except by their movements, that they were anything more than mere granules (see *m*, in Plate XII). At the same time active movement was more frequent than before.

I now thought it well to ascertain whether these minute and active bacteria would reproduce in urine the same sort of organism as that which we could not but believe to have been their parents in that fluid. On this occasion, having no more of the fresh urine, I adapted a syphon to a flask which was prepared on the 1st of March, and had furnished the material for numerous experiments, yet retained its original brilliancy as well as odour unaltered, was distinctly acid to litmus, and displayed no organisms under the microscope. Twelve hours after the inoculation on the 21st the liquid was already manifestly nebulous, and on examination with the microscope bacteria were found, four or five in every field, differing from those that had been introduced in being very rarely double but long and large and often curved (vide Plate XIII, *a*), having thus returned to a considerable extent to the condition before seen in urine, but now differing from their former state in that fluid in frequently exhibiting characteristic though languid movements. After twelve hours more the previous condition in urine was still more closely approximated by greater length in the segments, as illustrated by *b*, sketched because it happened to be at rest, though by no means having the longest unbroken segments that were observed. I now inoculated from this glass of urine another (*Urine III*) that had been decanted on the same day and had remained till then unchanged ; and twelve hours afterwards I sketched from this second glass the magnificent example of unjointed spirilliform organism represented at *h*. At the same time languid movement was seen in many specimens.

To complete the history of the behaviour of this organism in urine it may be added that, after the lapse of another fortnight, the bacteria in this glass were found again motionless and comparatively small, scarcely differing in appearance from those originally seen in the sour milk (vide foot of Plate XIII).

With the view of determining precisely the identity of the minute organism in the Pasteur's solution with the large one in urine, I stocked as follows, on the 21st of August, a 'glass garden' consisting of a massive piece of plate-glass excavated by the lapidary into a broad and deep ditch around a central island, the ditch to serve as a reservoir of air. This glass, together with a thin covering glass, had been exposed to a high temperature between metallic plates to diffuse the heat and avoid cracking, and cooled without access of dust. With heated forceps the covering glass was raised and, a minute drop of the Pasteur's solution with its organism having been mingled with a large drop of urine on a glass plate purified by heat, a little of the mixture was placed on the island. The covering glass was then luted down with melted paraffin, applied with a hot steel pen after a drop of water, boiled and cooled under the protection of carbolized cotton, had been placed in the ditch with the pipette to ensure a moist atmosphere. Immediately after this had been done I examined with the microscope and saw the minute bacteria of the Pasteur's solution as shown at *c*, in the Plate, in active movement. On looking again five hours later I found those bacteria replaced by large ones as seen at *d*, still moving though the movement was now languid. Within this short time the one variety of the organism had been converted into the other. Even if we supposed that the thick ones were of a different kind and that one of them had been present originally in the garden unobserved by me, their large numbers at the end of five hours and the vanishing of the small ones would be equally inexplicable. Hence, I think, we may regard it as demonstrated that the minute bacteria of the Pasteur's solution and the coarse ones of the urine were one and the same organism.

Other more remarkable facts, however, remain to be recorded. On the morning of the 22nd of August, wishing to ascertain whether this organism, after being so strangely modified in urine, in Pasteur's solution, and then again in urine, retained the property of inducing the lactic-acid fermentation in milk, I introduced a minute drop of *Urine No. II* into a second glass of milk decanted at the same time as the former, and which we may designate *Boiled Milk II.* Nine hours later test-paper already indicated a slight degree of acidity, and bacteria were found, five or six in each field, about as thick as those in the urine of inoculation, and also pretty long, generally single, but sometimes double as shown at *e*, Plate XIII. On looking at the same slide four hours later I found that other bacteria, much more minute and showing active progressive or rotatory movements, were also to be seen, and next morning such minute and active ones were alone discernible in another drop taken for examination. The acid reaction was now more marked, and the acidity continued afterwards to increase, till within three days the milk had set into a solid mass.

But along with the lactic-acid fermentation another and very different change took place in the milk during the first twenty-four hours. On first looking at the glass on the morning of the 23rd, twenty-one hours after inoculation, I was amazed to see at the bottom of the glass a deposit about a line in apparent thickness as black as pitch, showing out in a glaring contrast to the white milk. The black material did not appear to undergo any increase in the course of the day or at any subsequent period. But there was a peculiar sickly, almost putrefactive, smell mingled with the sour odour of the air in the glass shade in the course of the next twenty-four hours, though this afterwards passed off, and by the time that curdling was complete a pure smell of sour milk was alone perceptible. On the 26th I turned out the curd to investigate the black substance. I found it adhering firmly to the bottom of the vessel so that it could be completely cleansed of the curd with a camel's-hair brush without being detached ; and when I picked it out with a knife its lower surface had a brilliant polish, corresponding to that of the glass. It constituted a tough scale, between horny and leathery in consistence, and its upper surface presented numerous smooth round depressions with intervening ridges ; and it was plain that the pigment had been precipitated in the form of a heavy liquid, the particles of which had coalesced at the bottom of the vessel and afterwards solidified. The intensity of the colour was strikingly brought out by microscopic examination under my highest power, when even parts of extreme tenuity, as at *g*, Plate XIII, distinctly showed the sepia tint of the mass. These very thin parts also afforded the opportunity of ascertaining that the substance was perfectly homogeneous and structureless. In other words, the dark substance was not a coloured organism, but a pigment formed from the milk as the result of the growth of an organism in it. The small amount of the material at my disposal permitted me to ascertain only that it was insoluble in water, spirit of wine, anhydrous ether, and a strong solution of caustic potash, both in the cold and boiling states of these fluids, and was also unaffected by cold nitric acid, but was dissolved by boiling nitric acid, to which it communicated a yellow colour. Heated in a glass tube with access of air it burnt without fusion, leaving a white ash.

The question of course presents itself, what was the cause of this remarkable formation of pigment from the milk ? That it was induced by an organism introduced into the milk we cannot doubt. But was that organism the same bacterium that in the former glass of boiled milk, as in the original stock of unboiled milk, produced only the lactic-acid fermentation, but altered in function while modified in form by its residence in the other media, or was it some other species, some ' pigment bacterium ', to use Professor Cohn's expression, coexisting with the lactic-acid ferment ? Before discussing this question I must direct attention again to the glass of Pasteur's solution from which the second urine-glass was inoculated. It may be remembered that at the time of that inoculation there was already present a dingy or dirty aspect about that glass such as I had never before seen in Pasteur's solution. Next day this peculiar appearance was considerably increased, and on applying a pocket-lens, I discovered a number of minute dark brown specks disseminated over the glass, even close to the level of the liquid where the surface was vertical ; each brown point having a tiny brown streak extending downwards from it. I succeeded in picking up one of these brown specks with the attenuated end of the pipette, and on examination found it made up of a mass of motionless bacteria of ordinary form, themselves colourless, but having sepia-coloured particles disseminated among them of the same tint and intensity of colour as the pigment from the milk, very irregular in form and varying in size from mere points, much smaller than the bacteria, to masses considerably larger, as is seen at *n*, Plate XII, showing that the pigment, though produced under the influence of the bacteria, as seems clearly indicated by its existing specially among the bacteric masses, yet was, as in the milk, a mere amorphous and unorganized product. Thus, we trace back the pigmentary function to the Pasteur's solution, through the urine, although in the latter no pigment whatever was formed. This is in itself a point of interest, as indicating that the formation of pigment is not essential to the organism, but, just as in the case of the viscid substance produced under the influence of *Bacterium No. I*, occurs only when the medium in which the bacterium is growing is of a nature fitted for furnishing the requisite materials. Further the knowledge that the organism which produced the pigment was present in the Pasteur's solution and in the urine will aid us in considering the question whether that organism was or was not a different one from the lactic-acid ferment, and this we may now proceed to discuss.

Supposing it to have been a separate organism, it is not at all likely that it found its way by accident into the first urine-glass or the Pasteur's solution during the brief periods of exposure for inoculation or withdrawal of fluid for examination. For in no single instance have I known bacteria introduced before in this way. Nor can it have existed diffused through the original supply of milk, seeing that no pigment was produced in that stock or in the glass *Boiled Milk No. I* inoculated directly from it. We can only imagine it introduced from the original supply by supposing that it had entered the unboiled milk immediately before the inoculation of the first urine-glass, and was all taken up in the drop used for the purpose ; a contingency possible but not probable.

But even if we admitted that, in spite of the slenderness of the chance of such an occurrence, a separate 'pigment bacterium' had made its way accidentally into the first urine-glass or that of Pasteur's solution, we should find ourselves confronted by a further series of improbabilities. We should have to suppose that the two bacteria thus coexisting in the two fluids were both modified in form in the same manner by the two media, both becoming coarse and long-segmented in urine, and both minute and of ordinary bacteric aspect in the Pasteur's solution ; for none of the minuter kind were seen in the former fluid, nor any of the coarser sort in the latter. Further, we should have to suppose that the ' pigment bacterium ', when introduced into milk, grew with great activity for twenty-four hours and then suddenly perished. For we have seen that no further deposit of pigment took place after the first night, although the milk remained fluid considerably longer, and on microscopic examination of a drop from the upper part of the glass next day, when granular masses of caseine showed that coagulation had begun, I discovered not a vestige of pigment in it. And in further proof that the pigment bacterium, supposing such a separate organism to have been present, had died, I found that a bit of the curd introduced from this glass at the close of the third day into another glass of the same boiled milk, gave rise to the lactic-acid fermentation, pure and simple, with no formation of pigment, and none of the putrid odour that had attended the pigmentary formation in the other glass. It may, perhaps, be suggested that the ' pigment bacterium ' was poisoned thus early by the lactic acid generated under the influence of the other (supposed) organism. But unfortunately for such a view, we find the same transient character of the pigmentary function in urine as in milk. For, as has been before mentioned, the day after the inoculation of *Boiled Milk No. II* from *Urine II* (resulting in the pigmentary fermentation), I introduced a drop from *Urine II* into another glass of the same urine with the result of reproducing in great beauty the long unjointed form of the bacterium. After two days more I inoculated from this *Urine No. III* a fourth glass of the boiled milk, in the hope of getting back the pigmentary formation. But no such thing occurred, merely the lactic-acid fermentation. Now it is scarcely conceivable that the ' pigment bacterium ' (supposing it present) should have perished so quickly in the urine as well as in the milk. For it is to be remarked that the urine was but little changed by the bacteric development that followed the inoculation, retaining its acidity at the close of the two days, while little effect was produced upon its odour. Besides this it must be borne in mind that, if the supposed ' pigment bacterium ' was derived from the original stock of sour milk, it had before survived a residence for three days in urine, which was the fluid originally inoculated.

On the other hand, if we admit that there was only one organism present, but modified in function as in form by the different media, the course of events is exactly what we might have anticipated. It was in the Pasteur's solution that the pigmentary function first manifested itself, not indeed during the first thirty-six hours, during which it is distinctly recorded that the deposit in the glass was *white*, but in the course of the next day; and it is natural to suppose that it was in this medium, in which the form became so greatly modified, and at the same time the function of active motion conferred upon the previously motionless organism, that the faculty of pigmentary fermentation was also acquired. Then, just as modifications of form assumed by a bacterium in any one medium are more or less quickly lost when the organism is restored to its previous habitat, so should we expect it to be with altered function, and this bacterium, when transferred from the Pasteur's solution to either milk or urine, would more or less quickly lose the new fermentative property which it had acquired.

One clear instance of acquisition of a new function by the bacterium is presented by the power of active movement which showed itself for the first time in the Pasteur's solution; so that if we were to adopt the language of some authors who have attributed a most exaggerated importance to movement as a distinctive character, we should say that the organism was converted in that fluid from a bacteridium to a bacterium. But when restored to urine, the organism moved but languidly, and after about two days became again motionless. In milk, on the other hand, the power of motion was more permanently retained, and active movements were observed both in the third and the fourth glass of boiled milk as late as five days after the organism had left Pasteur's solution.

There is another consideration which seems strongly confirmatory of the argument against a distinct 'pigment bacterium' as the cause of the black deposit in the milk. If it were true that such an organism existed, which, when introduced along with the lactic-acid ferment, would produce this striking effect, black milk would be a thing of frequent occurrence; whereas this is, so far as I am aware, the first time such a thing was ever seen. But if it be asked, Why was it that this unheard of appearance showed itself in my experiment? the answer is that the conditions of the experiment were such as to afford the organism opportunities which it had probably never had before. Never before, in all probability, was this organism allowed to develop unmixed with any other in urine and Pasteur's solution consecutively. For while this ferment takes the precedence of others in milk, such is far from being the case in urine, and very probably in Pasteur's solution also. How far the previous residence in urine may have predisposed this bacterium to assume the pigmentary fermentation in Pasteur's solution, further experiment can alone decide. Suffice it to say, meanwhile, that the conditions under which the organism grew were novel, and therefore novel appearances need not surprise us. The case seems exactly parallel to that of *Bacterium No. I.* Never before, perhaps, was milk converted into so viscid a material as it was under the influence of that organism, simply because other organisms which would have interfered with the viscous fermentation were for the first time excluded.

I have dwelt at what will, I fear, be thought tedious length upon this discussion, because the conclusion arrived at seems to me of extreme importance. For if the same bacterium may, as a result of varied circumstances, produce in one and the same medium fermentative changes differing so widely from each other as the formation of lactic acid and that of black pigment in milk, it becomes readily conceivable that the same organism which under ordinary circumstances may be comparatively harmless, may at other times generate products poisonous to the human economy. We can understand, for instance, a thing that has at an earlier period of my practice as a surgeon often puzzled me, though now, happily, under the antiseptic system of treatment, I never have occasion to witness it, viz. the development of hospital gangrene beneath dressings left for a long time unchanged, whereas in the same hospital ward sores dressed daily continued healthy. Assuming what analogy leads us to suspect, that some organism is the cause of the disease, why should the special virus of hospital gangrene become introduced into a sore under the former condition more than under the latter? We now see that it is not essential to assume the existence of a special virus at all, but that organisms common to all the sores in the ward may, for aught we know, assume specific properties in the discharges long putrefying under the dressings. Similarly, we can imagine the unhealthiness of an old uncleansed hospital as caused not by the introduction into it of new organisms, but by a modification of those common to it and to freshly built institutions. I take these illustrations from surgery; but to the medical reader others of equal importance will readily suggest themselves from physic.

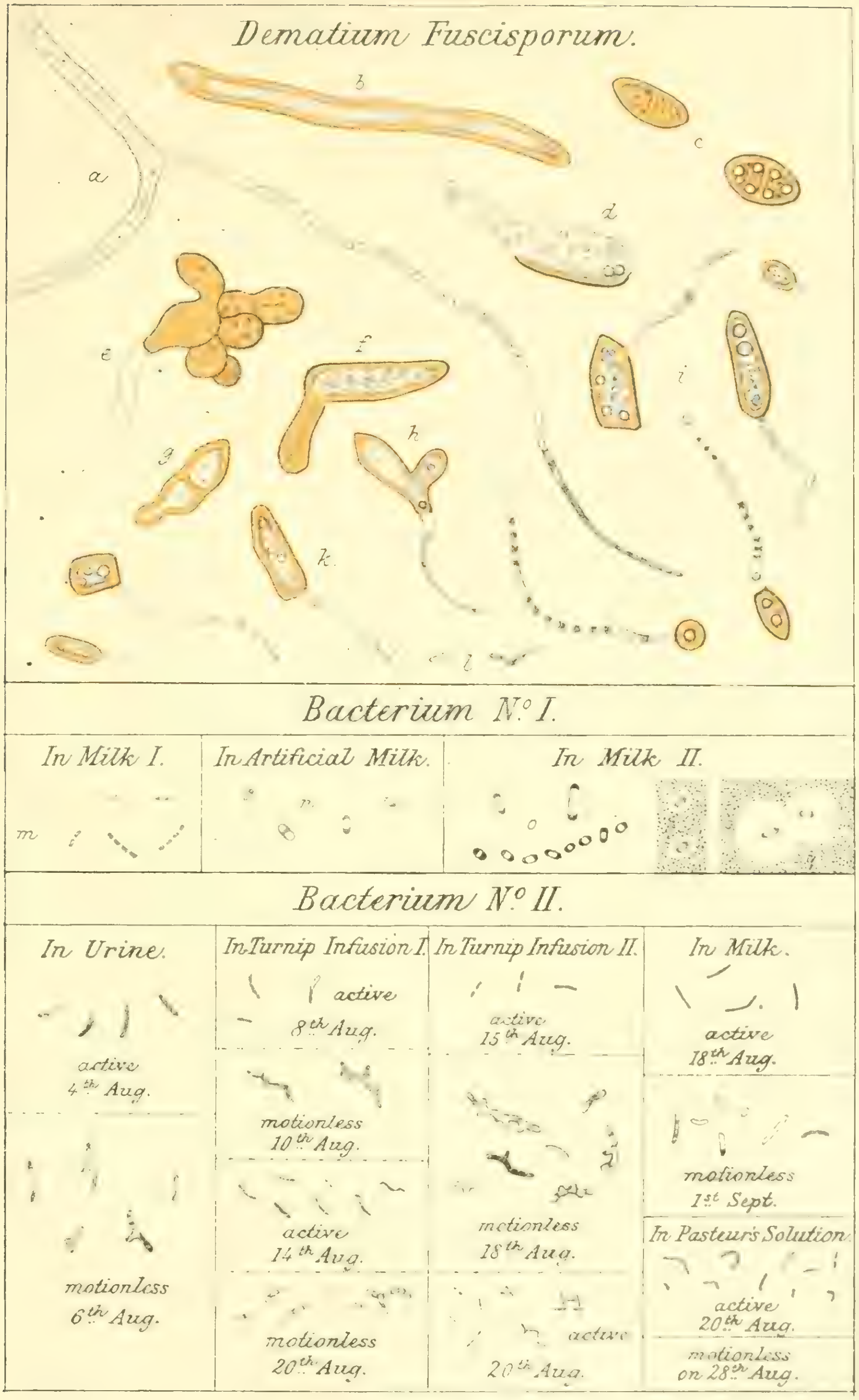
Another peculiarity of the glass of Pasteur's solution remains to be mentioned besides the formation of pigment in it, viz. a *putrid* smell which I never observed before in that fluid, and at the same time, a remarkable taste, a combination of slight bitterness with astringency, the latter so marked as to lead me to test for gallic or tannic acid with a persalt of iron, though without effect.

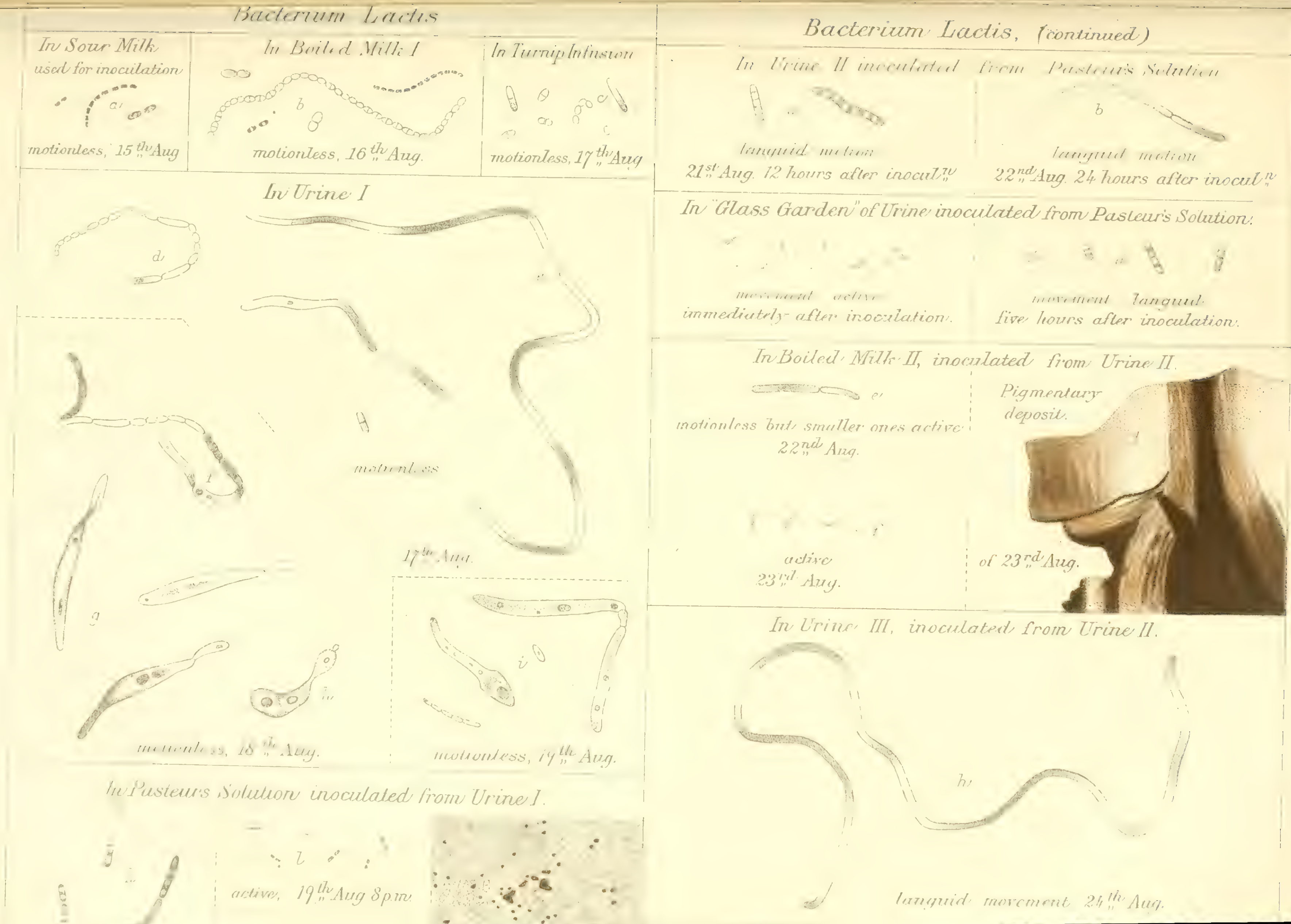
Admitting then that we had here to deal with only one bacterium, it presents such peculiarities both morphologically and physiologically as to justify us, I think, in regarding it as a definite and recognisable species for which I venture to suggest the name *Bacterium lactis*. This I do with diffidence, believing that up to this time no bacterium has been defined by reliable characters. Whether this is the only bacterium that can occasion the lactic-acid fermentation, I am not prepared to say; but it seems most unlikely that any other kind will be found combining all the peculiarities of that which we have studied. What fungus it is derived from, if, indeed, it have come from any (for it would be rash to assume that such an origin is universal), I have no means at present of knowing; but, however that may be, it cannot but be right, where we have definite characters of bacteria, to speak of them as species as a matter of convenience, just as is done of various hyphomycetous fungi known to be only inferior varieties of ascomycetous forms.

What are the functions of bacteria with reference to the physiology of fungi, and whether a bacterium derived from a fungus is ever capable of returning to the form of its parent, are questions on which my investigation has thrown no light.

The sketches which furnished the illustrations were all drawn on the scale given at the foot of Plate XIII, either by camera lucida or, in a few cases where the objects were in motion, by eye-piece micrometer, the magnifying power being 1,140 diameters. The object-glass which I employed was a tenth immersion lens manufactured by Messes. R. and J. Beck, the beautiful definition of which was distinctly enhanced by the use of the higher eye-piece.

Plate XI


Dematium Fuscisporum.
a
b
c
d
e
f
g
h
i
k
l
Bacterium No. I.
In Milk I.
m
In Artificial Milk.
n
In Milk II.
Bacterium No. II.
In Urine.
active
4th Aug.
motionless
6th Aug.
In Turnip Infusion I.
active
8th Aug.
motionless
10th Aug.
active
14th Aug.
motionless
20th Aug.
In Turnip Infusion II.
active
15th Aug.
motionless
18th Aug.
active
20th Aug.
In Milk.
active
18th Aug.
motionless
1st Sept.
In Pasteur's Solution.
active
20th Aug.
motionless
on 28th Aug.



Bacterium Lactis
In Sour Milk
used for inoculation
a
motionless, 15th Aug
In Boiled Milk I
b
motionless, 16th Aug.
In Turnip Infusion
c
motionless, 17th Aug
In Urine I
d
motionless
17th Aug.
g
motionless, 18th Aug.
i
motionless, 19th Aug.
In Pasteurs Solution inoculated from Urine I.
l
active, 19th Aug 8 p.m.
Bacterium Lactis, (continued)
In Urine II inoculated from Pasteur's Solution
b
languid motion
21st Aug. 12 hours after inocul.n
languid motion
22nd Aug. 24 hours after inocul.n
In "Glass Garden" of Urine inoculated from Pasteur's Solution.
movement active
immediately after inoculation.
movement languid
five hours after inoculation.
In Boiled Milk II, inoculated from Urine II.
e
motionless but smaller ones active
22nd Aug.
Pigmentary deposit.
f
active
23rd Aug.
of 23rd Aug.
In Urine III, inoculated from Urine II.
h
languid movement 24th Aug.

ON THE NATURE OF FERMENTATION

The Introductory Address delivered in King's College, London, at the Opening of the Session October 1, 1877.

[*Quarterly Journal of Microscopical Science*, April 1878.]

GENTLEMEN.—In making my first appearance as a teacher in King's College, I cannot refrain from expressing my deep sense of the honour conferred upon me by the invitation to occupy the chair which I now hold ; and, at the same time, my earnest hope that the confidence thus reposed in me may not prove to have been misplaced.

In considering how I could best discharge my duty as the person selected to deliver the Introductory Address of the Medical Session, I have felt that two courses were open to me : either to spend the short but important time at my disposal in an endeavour to convey to the student some sense of the exalted privileges, and correspondingly high responsibilities, of the beneficent calling to which he proposes to devote himself, or to treat on some special subject, in the hope that I might say something which should have interest, and, if possible, even instruction, not only for the student, but also for the eminent men whom I have the honour to see around me. The latter is the course which I have decided to follow, and the subject which I have selected is a short account of an inquiry in which I have been engaged in the interval between the cessation of my official duties in Edinburgh and their commencement here. The object of that investigation was to obtain, if possible, some more precise and definite knowledge of the essential nature of a class of phenomena which interest alike the physician, the surgeon, and the accoucheur. I allude to the changes in organic substances which are designated by the general term *fermentation*.

In medicine, the large class of diseases termed zymotic derive their name from the hypothesis that their essential nature is fermentative. In obstetrics, puerperal fever, the most frequent cause of disaster after childbirth, is now regarded by many of the highest authorities as likewise due to fermentative disorder ; and, in surgery, among the various causes which may disturb a wound, we know that by far the most frequent in operation, and the most pernicious in its effects, both upon the wounded part and upon the constitution, is putrefactive fermentation. If this be so, it is clear that to understand the nature of fermentation must be a matter of the very highest importance, with a view to curing or preventing the various evils to which I have alluded.

What, then, do we mean by fermentation ? I shall best approach the answer to this question by giving an example. Rather more than a week ago, I witnessed in the north of Italy the time-honoured practice of treading grapes in the wine-vat. I was told that the juice would within twenty-four hours boil, as it was said, over the vats into which it was introduced ; in other words, that the sugar of the grape-juice would within that short time be so converted into alcohol and carbonic acid that the carbonic-acid gas, by its evolution, would cause sufficient frothing to produce the effect to which I have referred. This conversion of the sugar of the grape into alcohol and carbonic acid is accompanied by the development of a microscopic organism, the yeast plant, or, to continue the old nomenclature, *Torula Cerevisiae*, consisting of microscopic cells multiplying by pullulation, as indicated in this diagram (not here represented) Now, it is, I believe, universally admitted that the alcoholic fermentation o grape-sugar is due to the growth of the yeast plant. M. Pasteur thinks that he has traced the origin of the yeast plant in the juice of the grape to a minute fungus adhering to the outside of the skin of the grape.[1] Be this as it may, it is admitted on all hands that the alcoholic fermentation is caused by the growth of the yeast plant. So long as the juice of the grape is protected by the skin of the berry, no fermentation occurs ; but, as soon as it escapes from that protection, the organism, by its development, induces the fermentation. Nor is it by any means exclusively in the natural juices of fruits that such fermentation occurs. Any sugary solution, provided it contains, besides the sugar, other ingredients requisite for the nutrition of the yeast plant, will serve as pabulum for the organism, and in that case the yeast plant will give rise to the fermentation. Here is a glass containing such a liquid, termed Pasteur's solution, because it was devised by M. Pasteur for the very purpose of affording nourishment to the yeast plant and other minute organisms. This was prepared on the 7th of August in a flask purified by heat, covered over with a cap of pure cotton-wool,[2] which allows the entrance of air, but does not permit the access either of the yeast plant or of any other form of dust. The Pasteur's solution, containing, besides sugar, ammoniacal and earthy salts for the nutrition of the fungus, was heated to about the temperature of boiling water, so as to destroy any organisms that might exist in the water. The result is, that it continues perfectly unchanged, just as it was on the 7th of August ; but, if we were to add to it a little of the yeast plant from fermenting grape-juice, we should find that, at the temperature of summer weather, it would very soon be in a state of free fermentation at the same time that the yeast plant would multiply. This, then, is a typical instance of fermentation. We have an active agent termed the ferment, which

[1] Vide Pasteur, *Études sur la Bière*, pp. 150 sqq.

[2] The cotton-wool was rendered free from living organisms by soaking it with a solution of carbolic acid in one hundred parts of anhydrous ether and allowing the ether to evaporate, leaving the carbolic acid behind in the cotton.

ferment is capable of self-multiplication. That I believe to be the essential property of a true fermentation. Now, in this particular case, I have already said it is admitted on all hands that the yeast plant is the cause of fermentation. Persons may differ as to how the development of the yeast plant gives rise to the resolution of the sugar into the alcohol and carbonic-acid gas ; but all now agree that, somehow or other, the organism causes the fermentation. Now, is it the case that all true fermentations are caused by the development of organisms ? That, gentlemen, is the question which it is desirable that we should be able to answer.

Take, for example, the case of the putrefactive fermentation of blood. We all know that, if blood be shed from the body into any vessel without special precautions, in a few days it putrefies. The bland nutrient liquid, soon after leaving its natural receptacle, becomes foul, acrid, and poisonous ; a change fully as striking as that which grape-juice undergoes in the alcoholic fermentation. Here, on the other hand, we have a vessel (a liqueur-glass) into which blood was received with special precautions. In the first place, the glass, covered, as you see, with a glass cap and a glass shade, with a view of preventing the access of dust, and standing upon a piece of plate-glass, had been heated to about the temperature of 300° Fahr., and cooled with an arrangement which ensured that the air which entered during cooling was filtered of its dust ; so that we were perfectly sure that the glass contained at the outset no living organisms.

Then, in the second place, the glass had been charged from a flask like this, provided with a spout. It contains, as you see, a glass tube introduced into it ; it is stuffed well with cotton-wool between the neck of the flask and the tube, there is a piece of cotton-wool over the end of the tube, and another piece is tied securely over the spout of the flask. The flask so arranged was heated just as the glass had been heated. It is not necessary to have the temperature so high as to singe the cotton. Heat far short of this is adequate, according to my experience, to make perfectly sure that you destroy all living organisms. The flask having been thus prepared, the jugular vein of an ox was exposed and divided, with precautions against the entrance of anything putrefactive,[1] and, the cotton cap having been taken off from the end of the tube, the vein was slipped over the tube and securely tied on, and then the hand of the assistant, who previously restrained the flow of blood, being relaxed, blood was permitted to flow into the flask. Then, before coagulation had time to take place, this and various other similar glasses were charged after the removal of the cotton cap from the end of the spout. Now, the first thing that may strike you is the

[1] This was secured by washing the skin and the instruments with a strong solution of carbolic acid (1 to 20), and performing the operation under a carbolic spray.

remarkable fact that this blood-clot has not undergone any contraction. One of the earliest things that your professor of physiology will have to teach the junior students will be that blood, after coagulation, contracts; that the fibrine of the coagulum shrinks and the serum is pressed out. But here no such thing has taken place. There has been no shrinking of this clot, no pressing out of the serum, and I venture to say that there is no one here—at least I think it is unlikely that there is any one here except myself—who has seen such a phenomenon, illustrating how, when the most familiar objects are placed under new circumstances, the most unexpected results may arise. Now, this is a matter of very considerable interest with reference to the behaviour of blood-clots inside the body in wounds and so forth. However, that is not a point on which I wish to dwell on the present occasion.[1] The point to which I wish to draw your special attention is, that this blood, although it has been six weeks in this glass, without any close fitting of the glass shade or the glass cap, and therefore with free opportunity for the access of the gases of the atmosphere, has not putrefied. The air in the glass shade is perfectly sweet, perfectly free from odour.

Now, gentlemen, this, without going further, is a very important matter. It proves that the blood has no inherent tendency to putrefaction. It further proves that the oxygen of the air is not able to cause the blood to putrefy, as used to be supposed. There was a time—the effect is still seen to a certain extent—when the dark venous colour of this blood-clot gave place to the crimson colour of arterial blood in a gradually deepening band from above downwards. We still see some of the red colour remaining, though now the converse effect has begun to take place. That florid redness, gentlemen, showed that the oxygen of the air was in reality acting upon the blood, yet it did not putrefy. Now, if I were to take a little morsel of already putrefied blood, say, upon the end of a needle, and touch with it this clot of blood, putrefaction would, in the course of a very short time, spread throughout the mass. Exactly as in the case of alcoholic fermentation under the influence of the yeast plant would the fermentation spread.

Putrefaction, then, is a fermentation, a true fermentation, characterized by the power of self-multiplication of the ferment. Then, gentlemen, if we examine microscopically, we find in the putrefying blood, as we found in the fermenting grape-juice, microscopic organisms, termed *bacteria* from their rod-shape, which we have represented in this diagram on the same scale as we had the yeast plant; of different sizes, but all very much more minute than

[1] I desire to guard myself against being supposed to express any opinion here as to the cause of this phenomenon.

the yeast plant, and commonly endowed with a remarkable power of locomotion. I say that, in the putrefying blood, we find these organisms developing *pari passu* with the fermentation.

Now, the question is, Are these bacteria the cause of the putrefactive fermentation, or are they merely accidental concomitants? These are two views which are entertained at the present day by men of high eminence. It may be said, 'Why should there be any doubt that the bacteria are the cause of the putrefactive fermentation, any more than there is a doubt that the *Torula Cerevisiae* is the cause of the alcoholic?' Well, one reason I believe to be that the bacteria are so exceedingly small. They are not so easily defined as the yeast plant. We cannot get them in a mass as we can get a mass of yeast; at least without a great deal of trouble; and, besides that, they occur very similar in appearance in a great number of different fermentations. There is, therefore, so far some colour for doubting whether bacteria are the cause of a special fermentation, like this putrefaction. Then there is another ground justifying such a view; for certain it is that organic substances are liable to extremely remarkable alterations, decompositions, under the influence of agents which are endowed with no life at all. As good an example of this as we can take is what occurs in the bitter almond when it is bruised with water. You all know what takes place under those circumstances; that there is prussic acid developed, and essential oil of almonds, with other materials. Now, these did not exist beforehand in the almond, but they are the result of the mutual action upon each other of two constituents, neither of which was hydrocyanic acid nor oil of bitter almonds, &c. These two constituents are termed emulsin and amygdalin. Amygdalin can be got from the almond in the form of definite crystals; and emulsin, though not a crystallizable substance, but a variety of albumen, can also be obtained separate. Till these two materials are in a state of solution in water, they do not act upon each other at all; but, as soon as they are in watery solution, the emulsin so acts upon the amygdalin that the latter becomes broken up into the constituents to which I have referred. This is an exceedingly remarkable fact. Undoubtedly, the emulsin is dead; there is nothing living about it. It is not an organism. It is obtained by a process of alcoholic extraction, and so forth. It is thoroughly a chemical substance, a merely dead substance, if we may so speak, and yet it does produce this remarkable effect upon the amygdalin. But, when we come to consider this case, we find that the process, remarkable as it is, lacks the true character of genuine fermentation, that of the faculty of self-propagation of the ferment. Liebig himself, who was the great advocate of the doctrine of so-called chemical ferments, and who, along with Wöhler, discovered this action of emulsin on amygdalin, pointed out, and showed by irrefragable evidence, that the emulsin does not undergo any multiplication ; not only so, but that, after a while, the emulsin loses the property of acting on the amygdalin : but, for a considerable time, it continues to act upon it without undergoing apparently either increase or diminution of its bulk. It may be called a resolvent, the amygdalin being the resolved material.

There are other cases equally striking that might be mentioned, not only in the chemistry of vegetables, but in the chemistry of our own bodies. There exists, for instance, in the saliva a material called ptyalin, which has a remarkable power of acting upon starch, so as to convert it into soluble compounds. In the gastric juice there is a material called pepsin, which has an equally remarkable property of acting on albuminous materials, fitting them for solution in digestion. But here again we find, when we come to consider the matter, that there is no evidence whatever that either pepsin or ptyalin is capable of self-multiplication. Each is secreted for the purpose and in the quantity in which it is required, but it has no faculty of self-propagation ; and I believe, if you search through the whole range of organic chemistry, you will not find a single established instance where any ferment, so called, destitute of life has been proved to have the power of self-multiplication. At the same time, gentlemen, it may be admitted that the thing might be theoretically possible. It is conceivable, for instance, that a resolvent, if we may so speak, of comparatively simple constitution might, by its action upon a resolvable compound, resolve it into substances, one of which should itself be the resolvent, and, if that were so, the process might go on *ad infinitum*. That is conceivable ; and accordingly, although we have no instance of the kind on record, yet we have persons in high authority, as teachers both of physiology and of pathology, maintaining the view that in putrefactive fermentation, for instance, the bacteria are probably mere accidental concomitants ; that the real essential agent in the putrefaction is not an organism at all, but some so-called chemical ferment destitute of life. And so long as we have authorities maintaining such a view, it is necessary to test its truth or falsehood by searching inquiry ; and such has been the object with which my investigations of the last two months have been conducted.

As regards the putrefactive fermentation, we have already evidence in the flask and in the glass that I have shown you (the flask also has no putrefactive odour emanating from it), that blood has in itself no inherent tendency to putrefy. It must receive something from without, and that something is not mere oxygen or any other atmospheric gas. I have now to point out to you that the addition of water is not of itself sufficient to induce this fermentation. Blood and water constitute a mixture highly putrescible, very much more so than blood itself. But in this flask we have had mixed with water the contents of one of the liqueur-glasses of unputrefied blood like that before shown to you. The water, however, had been previously boiled, so as to kill any organisms in it ; boiled and cooled under the protection of a cotton cap, and then, the cotton cap being raised, careful provisions (into which I must not enter) against the entrance of dust being taken, the clot was spooned into the water ; a fresh cotton cap, perfectly pure, was put on, and so we got, I believe for the first time, a permanent cold watery extract of blood, and here it retains the same brilliant clearness that it had in the first instance, more than a month ago. Mere water, therefore, is as inadequate to induce the putrefactive fermentation of blood as are the gases of the air.

But the fermentation which I have been especially investigating has not been the putrefactive, but one which seemed to me more convenient for the purpose, the lactic fermentation, by means of which milk sours and curdles, through conversion of the sugar of milk into lactic acid. This is a curious instance of a chemical transformation. The composition, as regards the proportions of the three elements, carbon, hydrogen, and oxygen, remains identically the same ; but those of you who are chemists understand what I mean when I say the atomic weight of the lactic acid is one fourth of the atomic weight of the sugar of milk. Each atom of milk-sugar is resolved into four simpler atoms of lactic acid. Now, it may be naturally supposed, if you observe what happens in a portion of milk obtained from a dairy, that there is an inherent tendency in the milk to this souring and curdling. If you get milk from a dairy and keep it long enough, it is certain to turn sour and curdle : then, after a while, there comes a certain mould upon the surface, the *Oidium lactis*, which constitutes the sort of bloom there is upon a cream cheese ; then comes on, often simultaneously with the growth of this mould, the butyric fermentation, in which butyric acid is produced ; and afterwards, if you keep the milk long enough, it will probably putrefy. When you see, time after time, specimens of milk, taken from various dairies, undergo this succession of alterations, you may be tempted to suppose that these were changes to which the milk was disposed from its own inherent properties as it comes from the cow's udder. The late eminent Professor of Chemistry in this College, Professor Miller, in his excellent work on Chemistry, states that the ferment of the lactic-acid fermentation is the caseine of the milk. I am bound to say, however, in justice to Professor Miller, that he also adds that M. Pasteur has expressed his belief that there exists an organic living ferment which produces this fermentation ; but Professor Miller does not profess to decide between these two opinions. On the contrary, his first statement, that the caseine is the ferment, might lead you to suppose that he is inclined to the former view.[1] If this were the case, as there is caseine always in the milk, there should always be the lactic-acid fermentation. But it was pointed out long ago by M. Pasteur that, if you examine any specimens of souring milk with the microscope, you find little organisms.[2] These, when you come to look at them carefully, you see to be obviously of the nature of bacteria. Bacteria may either have the faculty of motion or they may not. This particular bacterium is a motionless bacterium, so far as I know ; still it has the essential nature of a bacterium : a microscopic fungus, multiplied by fissiparous generation, the lines of segmentation being transverse to the longitudinal axis of the organism. I have ventured to give to this little organism the name *Bacterium lactis* ; for, gentlemen, no doubt there are different kinds of bacteria. The circumstance that they are minute must not make us shut our eyes to this truth. You sometimes hear bacteria spoken of as if they were all alike. The fact that some do not move and others do, is one indication of a difference between them. Another indication of a difference is, that some bacteria will thrive in a medium in which others cannot live. For instance, the *Bacterium lactis* refuses to live at all, according to the more careful experiments I have been lately making, in Pasteur's solution ; the very fluid provided by Pasteur for bacteria, torulae, and other fungi to live in, is a medium in which the *Bacterium lactis* refuses to grow at all ; although many bacteria grow in it with rapidity. That is clear evidence that this is a different kind of bacterium from those which both thrive and move in Pasteur's solution. You will observe, also, it is somewhat peculiar in the form of the segments ; they are oval, and not so rod-shaped as bacteria generally. These you will always find in milk when it is souring.

But, gentlemen, neither the souring of milk nor the organism which is found associated with that change is the result of any inherent tendency in the fluid. This is a flask of boiled milk prepared on the 27th of August, with the same arrangements for ensuring purity of the vessel and excluding dust that we had in the flask of Pasteur's solution. It has not coagulated ; it has undergone none of the changes to which I have alluded. There has been no butyric fermentation, no *Oidium lactis* has formed upon it, no putrefaction has occurred. This milk is as sweet as when it was first prepared ; and if you were to examine it with the microscope, you would find in it no organism of any kind. From this same flask, with precautions with which I will not detain you, I have charged

[1] Vide Miller's *Elements of Chemistry*, third edition, vol. iii.

[2] Vide 'Mémoire sur le Fermentation appelée Lactique', *Annales de Chimie et de Physique*, 3me série, tome lii, 1858.

various purified liqueur-glasses. This one has been charged for more than four weeks, yet the milk remains fluid, you observe, although there is abundantly free access of air to it The oxygen of the air and the caseine which still exist in the boiled milk have together been unable to bring about the lactic fermentation. As regards boiled milk, this is sufficient evidence that the lactic fermentation is not something to which the liquid is spontaneously prone ; it requires something to be introduced into it from without. For you must not suppose that the boiling has rendered the milk incapable of souring. All that it requires is the introduction of the appropriate ferment. If you were to touch the edge of the milk in this glass with the point of a needle dipped in souring milk from a dairy, within two or three days the whole would be a sour clot, showing both the proneness of boiled milk to souring and also the genuine fermentative character of that change as indicated by the faculty of self-multiplication of the ferment. And on microscopic examination you would be sure to find the *Bacterium lactis* present throughout the mass.

But though the ferment which occasions the souring of milk is present in the milk obtained from any dairy, it appears to be by no means common in the world in general. Suppose you take a series of glasses of boiled milk like these, and introduce into them a series of drops of ordinary unboiled water, you will get fermentation in them. If you put into each, for instance, a drop as large as a quarter of a minim, you will have a fermentation in every one, and an organism in every one ; but you will neither have, according to my experience, the lactic-acid fermentation nor the *Bacterium lactis*. You will have bacteria of other sorts ; fermentations of other kinds. Again, suppose you take a series of such glasses, take off the glass shades and the glass caps, in different apartments or at different times, and expose the milk to the air-dust for half an hour ; you will get fungi and bacteria of various sorts, but, according to my experience, you will not get the *Bacterium lactis* ; nor will you get the lactic fermentation. And thus it turns out, so far as boiled milk is concerned at all events, that the ferment that brings about this particular fermentation is a rare ferment. So far from boiled milk being spontaneously prone to the change, it requires something to be introduced from without which is a rarity both in ordinary water and in ordinary air.

But then, it may be urged, indeed such arguments have been used, this may be very true for boiled milk, but how about unboiled ? 'May it not be that, by boiling the milk, you have destroyed certain chemical ferments, purely hypothetical we must admit, but which we think likely to exist ?' For, according to the views of some persons, it may be that in the unboiled milk there may exist certain chemical substances prone to evolve into organisms by spontaneous generation, and prone to produce these and other fermentations, but which, by the act of boiling, we deprive of this tendency. Therefore, with a view to meeting this objection, the first part of my investigation was devoted to endeavouring to see whether or not milk, as it comes from the cow, really does or does not contain materials tending to the development of organisms or to fermentation of any kind.

An exceedingly simple experiment will probably serve to convince you to a considerable extent with regard to this matter. If you go to a dairy where there is also a cow-house, take a couple of clean bottles, and fill one with milk from a pan in the dairy and the other with milk direct from the cow in the cow-house, the milk obtained from the dairy will be certain to sour, but that which you get direct from the cow will very probably never sour at all. It will probably acquire a nasty bitter taste, and will not contain the *Bacterium lactis* or the *Oidium lactis*, but some other kinds of fungi. That very simple experiment is enough to show that the lactic-acid fermentation is not a change to which unboiled milk is spontaneously prone. And it occurred to me that, if all organisms and fermentations which occur in milk really depended on accidental introduction from without, by performing the experiment with a number of purified glasses and taking the milk in small quantities into each, we might by thus subdividing elude the foreign element and get the milk, in some of the glasses at least, not only without the lactic-acid fermentation or the *Bacterium lactis*, but without any fermentation or any bacterium, or any sort of organism. Accordingly, I prepared little glasses like these ; little test-tubes with test-tube caps, arranged upon a stand made of pieces of glass tube and silver wire. The stand containing the test-tubes was placed under a glass shade on a plate of glass and purified by exposure to 300° Fahr. in the hot box. Milk having been received from the cow into a purified vessel, some of the milk was then, by means of a syringe attached to this pipette (the pipette having been also previously purified), drawn up into the pipette, and then, by means of the syringe, each little cap being in succession raised, a few minims of milk were introduced into each of the glasses, the caps being immediately reapplied. The result was, every one of the milks underwent fermentation, and every one of them contained organisms, some of them as many as three different species. The great majority of those twelve glasses presented little orange specks, such as were never seen, I suppose, in any milk before ; and, on examining these, I found them to be little organisms belonging to a group to which I have ventured to give the name Granuligera, because they consist of granules, different from bacteria in this respect, that you might suppose them not to be organisms at all till you had the opportunity of seeing them undergoing multiplication by fissiparous development, in a manner, however, differing from the transverse fissiparous multiplication of bacteria, in being crucial.[1] But, besides the granuligera, there were among the contents of these test-tubes bacteria of different kinds, to judge by form and size, and in one of them was a toruloid organism, and in two others two species of filamentous fungi, one of which was of the most exquisite delicacy, though in general type of the same sort of arrangement as the common blue mould or the *Oidium lactis*. The size of the filaments was so exceedingly small that twenty of them would lie abreast in a single human red corpuscle ; they were smaller in diameter than even the *Bacterium lactis*, smaller than the great majority of bacteria. I doubt if any such exquisitely delicate filamentous fungus has ever been seen before even by a professed botanist like my colleague Professor Bentley. But there was no *Bacterium lactis*, and there was no lactic-acid fermentation.

What inference were we to draw ? Was I to suppose that, although the lactic-acid ferment had been excluded, it was impossible to exclude others ; that others were present in the milk as it existed in the cow's udder ; or was it that I had not been sufficiently careful ? The latter was the view I was disposed to take. The experiment had been performed in the cow-house, where certainly the air might be supposed to be reeking with organisms. I therefore performed the experiment a second time, and this time in the open air. It must be confessed it was not far from the cow-house, and it was a fine day at the very time of the year in which organisms most abound. On this occasion, I used twenty-four of the little covered test-tubes ; those which you see before you. The result was that this time, again, every glass had organisms developed in the milk which it contained. At the same time, every glass seems to be different from all the rest. Such fermentations as there are here, I venture to say, were never seen in milk before. I have brought before you a diagram, showing some of them on a large scale. I want particularly to direct your attention to these strange scarlet spots which occurred in almost all of them. They began as tiny scarlet dots, which spread as fermentative changes capable of self-multiplication in the substance of the milk. Here is one glass that is green, and here is another of an orange-yellow colour. Here are two that have two kinds of filamentous fungi. I have not examined them microscopically, but I shall very likely find there are some species that have not been described.

I felt little doubt that these organisms had got in for want of sufficient care on my part. But how are we to explain these unheard-of appearances ? Simply thus. If the *Bacterium lactis* had been here, it would have taken the precedence of all other organisms in its development, and the changes which it would have

[1] Vide *Transactions of the Royal Society of Edinburgh*, vol. xxvii, p. 319 (page 281 of this volume).

induced would have made the milk an unfit soil for these other numerous species. And the novelty of the appearances depended not on the presence of an unusual variety of organisms, but merely on their having enjoyed an unprecedented opportunity for coming forward. Under ordinary circumstances they would have been smothered—killed—by the effects of the *Bacterium lactis* and the other ferments that commonly develop in its wake. Such being my belief, I determined to make one more attempt. This time I used again the original twelve glasses, but charged them with greater care. I mentioned that a large proportion of these glasses of the second experiment had scarlet spots; and in the former experiment in the cow-house the great majority had orange spots, and those, as we have seen, were composed of heaps of granules. It occurred to me that one cause of failure might be this. Suppose one single group of such granules to exist, and to become disturbed and broken up in the process of transference to the glasses, it might vitiate the whole specimen of milk; therefore, instead of drawing up the milk into the pipette with a syringe and then expelling it, I determined to have it introduced as directly as possible into the little glasses. With this object I employed these two glass tubes, connected together, as you see, with a short piece of india-rubber tubing, the wider tube being for the purpose of receiving the milk, the narrower to conduct it into the glasses. The glass tubes had been purified by a high temperature, and the piece of india-rubber connecting them, as it would not bear a very high temperature, had been boiled for half an hour. The same cow was taken out again into the open air, and this day the elements were in my favour. It had been a drizzly morning, and I might fairly hope that some of the multitudes of organisms existing in the little orchard might have been washed down and that the air might thus have been somewhat purified. I was also more careful in this respect. I got the dairywoman to milk the cow without drawing the hand over the teat, performing the operation by an action of the fingers in succession, so that the end of the teat should always be exposed. Her hands were washed with water, and the cow's udder also, and she having squirted out a little milk to wash away any organisms from the orifice of the duct, the glass cap which protected the larger tube from dust was removed and the end of the tube was held in the immediate vicinity of the teat; a few drachms were introduced, then the cap was readjusted, and then these little glasses were filled by the simple expedient of alternately relaxing and compressing with the finger and thumb on the caoutchouc, so that there was as little disturbance as possible of the organisms that might be supposed to be introduced in spite of my care. It is six weeks since this was done. At first sight, you might suppose, contrasting these appearances with those of the other tubes which were charged only three days earlier, that the milks of this last experiment were all pure. The truth is, all but two have organisms in them ; but I may mention that all but four had obviously organisms in them before I went for my trip on the Continent three weeks ago. On my return I found that in the course of the three weeks that had elapsed, two others had gone ; but they already showed organisms which, though very pale and insignificant, were quite easily seen by a magnifier in such considerable mass that I felt sure they must have already been growing for a considerable time ; and, therefore, in all probability those that still seemed to the naked eye and to the magnifier free from organisms were really so. Accordingly, two days ago I drew out milk from one of those that seemed to be still pure, and I had the great satisfaction of finding it not only perfectly fluid and tasting perfectly sweet, with a perfectly normal reaction, purpling both blue litmus paper and red litmus paper—the normal reaction of perfectly fresh milk—but under the microscope I could not discover any organism of any kind whatsoever. Therefore, I think we are justified in saying that in unboiled milk as in boiled milk, provided, of course, the cow be healthy, there does not exist any constituent having the power of giving rise to organisms or producing the lactic or any other fermentative change.

This, gentlemen, was the first step of the investigation : to the second I must beg your special attention, because I believe you will agree with me that it is by far the more important step of the two.

The object of the second part of the investigation was to find absolute evidence, if possible, whether the *Bacterium lactis* was or was not the cause of the lactic fermentation. It occurred to me that, if we could estimate with some degree of accuracy the number of bacteria present in a given quantity of souring milk, and then if we were to dilute the milk with a proportionate quantity of boiled water, we might have the diluted milk so arranged that every drop with which we should inoculate a series of glasses of boiled milk might contain, on the average, one bacterium ; and if we should do so, as it would be practically certain that the bacteria would not be distributed with absolute uniformity, we should expect that we might have, as the result of these various inoculations, some glasses with the *Bacterium lactis*, and some without it ; and, if it should turn out that all those glasses which contained the *Bacterium lactis* underwent lactic fermentation, and, on the other hand, those glasses which were free from bacteria had no fermentation, that would prove the point ; as, I think, you will agree with me, when we come to discuss the matter at a little more length after we have all our facts before us. Well, how were we to determine the number of bacteria existing in the liquid ? This was done in a simple manner. A circular covering glass, just half an inch in diameter, was used. Of course, we know how many square thousandths of an inch there are in the area of this little glass. We also know by the micrometer how many thousandths we have across the field of our microscope, and, therefore, by calculation we know how many square thousandths there are in our field, and thus we can tell how many fields there are in the covering glass. To measure the liquid, I used this little syringe, with the piston rod in the form of a screw, on which revolves a disc, graduated for 100ths of a minim; by which means you can, with perfect precision, emit 1–100th of a minim, or 2–100ths, or any number you choose. I found that 2–100ths, or 1–50th, exactly occupied the covering glass; so that, when it was put down upon a glass plate, with 1–50th of a minim interposed, the rim of fluid round about the covering glass was not one-quarter of the diameter of the field, using the highest magnifying power; so that practically the liquid was all under the covering glass. I knew, therefore, that there was 1–50th of a minim under the covering glass. If, then, I counted how many bacteria there were in a field, taking a number of different fields and striking an average, I could ascertain how many bacteria there were on the average in a field; therefore, by calculation, how many there were under the covering glass; or, in other words, how many there were in the 1–50th of a minim; and, consequently, I knew how much boiled water I ought to add in order that the drop, of whatever size I might wish it to be, should contain, on the average, one bacterium, and one only. This being done with a particular specimen of souring milk, I found that it was needful to add no less than one million parts of boiled water to the milk to ensure that there should be rather less than one bacterium, on the average, to every drop. Then with drops of that size I inoculated five glasses of boiled milk, and the result was that out of the five only one curdled; but one did curdle and soured, and that one had the *Bacterium lactis* in abundance; the others did not curdle, underwent no fermentation whatsoever, and had no bacteria in them. You may say, perhaps, 'How was it that there were none of these numerous different organisms and fermentations that you have been showing us?' Simply for this reason, that although many other kinds of organisms undoubtedly did exist in the milk, yet most of them were in exceedingly small proportion to the *Bacterium lactis*, so that you might have searched, perhaps, for a whole day, with the high power of the microscope which it was necessary to use, and never discovered one. We are apt to forget how difficult it is to find these minute objects with high powers of the microscope, unless they are very numerous indeed. Therefore, when we came to dilute the milk with a million parts of water, the chances of getting anything but the *Bacterium lactis* were exceedingly small. It was with reference to the *Bacterium* *lactis* that the dilution had been made, and not with reference to these other organisms relatively so rare. It happened that we saw in the souring milk before making the dilution that there was another kind of bacterium present, a moving kind different from the *Bacterium lactis*; it was in every field, but not nearly so numerous as the *Bacterium lactis*, and, consequently, it did not occur in the one milk that curdled.

Now, therefore, we had every reason to hope that we had got the ferment pure, and thus we had the opportunity of performing other experiments; and the last experiment that I shall mention is this. Having induced the lactic fermentation in another glass of pure boiled milk by means of our presumably pure ferment, and estimated the number of bacteria per minim, I diluted with boiled water accordingly and then proceeded as follows:—These five covered test-tubes which you see before you, containing boiled milk in their lower part, were inoculated each with a drop calculated to contain two bacteria; these other five similar test-tubes were inoculated each with a drop calculated to contain one bacterium; these five liqueur-glasses were also inoculated with drops each calculated to contain one bacterium; and one other liqueur-glass with a drop calculated to contain four bacteria. The result was that the specimen with the drop calculated to contain four bacteria soured and curdled in a few days; and all these five calculated to have two bacteria to a drop curdled also in a few days. The milk, you see, is perfectly solid. You will also observe that no change has taken place except the lactic fermentation, no *Oidium lactis* has grown, and no other alteration has taken place; it is as pure in whiteness as when it was first coagulated. I may here mention that, although all these glasses of milk coagulated, they did not do so at the same time. There was a time in the twenty-four hours during which the coagulation went on, in which I hoped that some of them were going to be permanently fluid, implying, as you would expect, that the particles of the ferment were not uniformly distributed; some had more than others, though each happened to have at least one. But, of the five test-tubes calculated to have only one bacterium on the average to each inoculating drop, three have remained fluid, and so have two of the liqueur-glasses; so that, of the ten calculated to have on the average one bacterium each, exactly five, it so happens, have remained fluid without any curdling. I may consider myself somewhat fortunate that I have succeeded in bringing these specimens all the way from Edinburgh in this condition. I will now deprive this one of the protection in which it has hitherto lived. [Mr. Lister, having removed the glass shade and glass cap from one of the liqueur glasses, proceeded to drink part of its contained milk.] It is perfectly sweet. It has a slight flavour of suet, which M. Pasteur has described as resulting from the oxidation of the oleaginous material of the milk. If any gentleman likes to taste it after the lecture, he can do so.

Let me note this curious circumstance, that, of those specimens which did coagulate, those in the tubes coagulated considerably earlier than those in the more open vessels. At first, it seemed as if, for some strange reason, those in the open vessels were going to remain permanently fluid—even that which had, according to the calculation, four bacteria to the drop. I presume this is to be explained on the same principle as Pasteur has explained a corresponding fact with regard to the yeast plant. He has shown that, if a saccharine solution be put in a very thin layer in an open vessel with yeast, the yeast plant develops very rapidly, but very little fermentation occurs; on the contrary, if it be put into a deep vessel, the development of the yeast plant does not go on so rapidly, but more fermentation results. He explains the fact in this way: that the yeast plant requires oxygen for its nutrition; if it gets it easily, as it does in a shallow vessel in the air, it produces comparatively little effect in breaking up the sugar into its constituents, and vice versa. So here, in the test-tubes the carbonic acid accumulated, supposing any to exist, as in a well, and the *Bacterium lactis* had but little opportunity for getting oxygen. Accordingly here, just as in M. Pasteur's experiments with a sugary solution with yeast in a deep vessel, the *Bacterium lactis* produced more rapidly its fermentative effect.

But this, you say, is assuming that *Bacterium lactis* is the ferment. Now we are coming to that point. But first I have to mention an additional fact. For the satisfaction of others rather than for my own, I went through the laborious process of investigating portions of the contents of all these vessels; and I found that, in every one in which the lactic-acid fermentation had taken place, where there was curdling and souring, the *Bacterium lactis* was present; and in no instance in which there was no lactic fermentation was any bacterium of any sort to be discovered. I believe that fact demonstrates that the *Bacterium lactis* is the cause of this very special lactic fermentation. Let us assume for a moment that there did exist some other material besides the *Bacterium lactis* in the milk capable of causing the fermentation; that the lactic ferment was not the bacterium at all, but some chemical ferment. First of all, you will please to observe that we have from this experiment absolute evidence that the ferment, of whatever nature, is not in solution, but in the form of suspended insoluble particles. If the ferment had been in solution, every equal-sized drop of the water of inoculation would have produced the same effect. The fact that some drops were destitute of the ferment proves that that ferment was not in a state of solution. That is absolutely demonstrated. Now, suppose we admit, for the sake of argument, that the lactic-acid ferment consisted of particles of some non-living substance, capable of self-multiplication as rapidly as the bacterium, but not living; a strange hypothesis, no doubt—but suppose we assume it. Suppose we admit that the true lactic ferment and the *Bacterium lactis* were merely accidental concomitants of each other, it would be absolutely inconceivable that these two accidentally associated things should be present in exactly the same numbers. And yet, according to the hypothesis, such would be only another mode of stating our observed fact, which amounts to this, that wherever there was a fermentative particle there was a bacterium, and wherever there was a bacterium there was a fermentative particle. But, suppose you admitted that—that there were exactly as many of the *Bacterium lactis* as there were of the hypothetical true fermentative particles—suppose you admitted that inconceivable thing, I say it would be again inconceivable that, if mutually independent, they should accompany one another in pairs, that invariably where there was *Bacterium lactis* there should be a ferment particle, and where there was no *Bacterium lactis* no ferment particle. That would be a thing as inconceivable as the other. Therefore, we have two inconceivables, one of which would have been sufficient to show that we cannot admit any other hypothesis than that *Bacterium lactis* is the cause of the lactic-acid fermentation.

But the experiment tends to even more than this. Where we find the effect so exactly proportioned, as regards the number of glasses affected with fermentation, to the adult bacteria that we count, we are led to infer that this particular bacterium, at all events, has not any spores—that there are no spores existing in addition to the bacteria. People seem often to assume that bacteria must necessarily have spores or germs. It seems to me an unlikely thing that they should. They are, as it were, a generative apparatus *per se*, they are constantly multiplying; why should they have spores? I do not say that bacteria may not have spores. There are very different kinds of bacteria; some may have spores, and some may not; but this sort of result seems to indicate that this particular bacterium has no spores; at least, in the condition in which it exists in souring milk; because, if we had, besides the bacteria that we can count, spores of bacteria disseminated through the liquid also, we should have the effect more than in proportion to the bacteria that we have counted. The only fallacy here is that it may be that the bacterium has not been diffused uniformly through the milk. Therefore, I do not say that in this case it is absolutely proved. But, at all events, this experiment gives us a line of inquiry, by means of which we may probably settle that point with regard to any individual case of bacterium. This, however, is a point I do not desire now to insist on; but what I do venture to urge upon you is, that you will seriously ponder over the facts which I have had the honour of bringing before you to-day; and, if you do so, I believe you will agree with me that we have absolute evidence that the *Bacterium lactis* is the cause of the lactic-acid fermentation. And thus I venture to believe that we have taken one sure step in the way of removing this important but most difficult question from the region of vague speculation and loose statement into the domain of precise and definite knowledge.

ON THE LACTIC FERMENTATION AND ITS BEARINGS ON PATHOLOGY[1]

[*Transactions of the Pathological Society of London*, vol. xxix, 1878.]

A FEW years ago it would have seemed very improbable that the souring of milk should have any bearings upon human disease; but all will now be ready to admit that the study of fermentative changes deservedly occupies a prominent place in the minds of pathologists.

In order that any sure steps may be taken to elucidate the real nature of the various important diseases which may be presumed to be of a fermentative nature, such as the specific fevers or pyaemia, the first essential, as it appears to me, is that we should have clear ideas, based upon positive knowledge, with regard to the more simple forms of fermentation, if I may so speak—more simple because they can be conducted and investigated in our laboratories.

It may be said, indeed, that such information has been already afforded us by the researches of Pasteur and others who have followed in his wake, tending to prove that all true fermentations of organic liquids are due to the development of organisms within them; and I confess that for my own part I am disposed to agree with that view. But this opinion is by no means universal in our profession. We meet with statements by men of very high position, both as physiologists and pathologists, to the effect that in various fermentations—such, for example, as putrefaction—the bacteria which are found to be present may, for aught we know, be mere accidental concomitants, not causes, of the fermentative change. And such being the case, it seemed desirable to obtain, if possible, entirely conclusive evidence upon the subject.

About four months ago I made an attempt of this kind with regard to the lactic fermentation; and I propose on the present occasion to bring forward the results arrived at, and at the same time to afford the members of the Pathological Society an opportunity of seeing with their own eyes samples of the preparations which resulted from that inquiry, and on which my conclusions are based.

First, however, I desire to describe my method of experimenting, which,

[1] This communication, made to the Society without manuscript, on the 18th of December, 1877, is here given in its original form. In preparing it for the press, however, matter has been introduced including some points into which the time at my disposal did not allow me to enter, and also some facts since ascertained, together with considerations arising from them.

in its present simplified form, has never been published. It is based, in the first instance, on the fact which experience has now amply demonstrated, that if we have a vessel like this liqueur-glass (A) in a state of purity, covered with a pure glass cap (B), the capped liqueur-glass being further covered with a glass shade (C), and standing as a matter of convenience on a plate of glass (D), any organic liquid contained in the liqueur-glass, provided it be free from living organisms at the outset, will remain without any organic development occurring in it as long as the arrangement of the glasses is left undisturbed. Or, in other words, although an interchange is constantly taking place between the gases

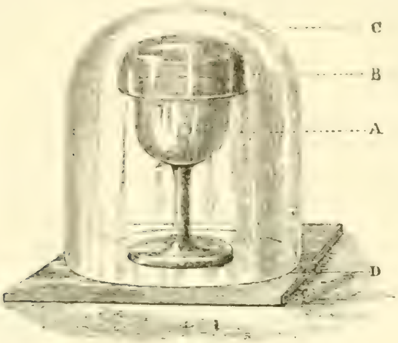


FIG. 1.

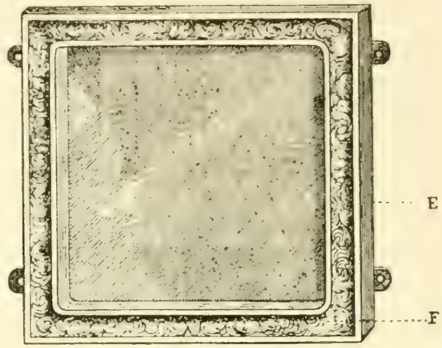


FIG. 2.

of the atmosphere and those in the liqueur-glass—for the cap does not fit at all, and the shade is not air-tight—yet the double protection of the glass cap and the glass shade effectually prevents access of the atmospheric dust to the liquid; and if the dust is excluded, organisms do not occur in it.[1]

The glasses are obtained pure by means of heat. I find that exposure to a temperature of 300° Fahr. for two hours is sufficient to deprive all living material of its vitality. But it is not enough that the glasses should be so heated; it is necessary that the air which enters them during cooling should be filtered of its dust. This I secure by heating them in a cast-iron box, the door of which (E) is here shown. This door has its circumferential part in the form of a groove, capable of being packed with a considerable mass of cotton-wool (F).

[1] A curious exception to this general truth was met with by Mr. Godlee in the course of his experiments made by this method upon the vaccine virus, recorded in the *Transactions of the Pathological Society*, vol. xxviii. He found that *Penicillium glaucum* made its appearance in some of his glasses in a way that seemed unaccountable, till he discovered that the cupboard in which the vessels were kept was infested with acari, and that these creatures crawled up and into the glasses. He further found, on examining some of these acari under the microscope, that spores of the Penicillium were to be seen actually adhering to their hairs. The wonder now came to be, not that that fungus should have entered the glasses, but that other organisms, such as bacteria, should not have been also carried in. If there were any reason to apprehend the intrusion of such creatures, they might no doubt be easily excluded by placing each glass plate in an ordinary dinner-plate containing glycerine, so as to surround the glass plate on all sides with the viscid liquid.

The door can be screwed by means of nuts (G, Fig. 3) against the edge of the box (represented by dotted lines in the sketch); and the cotton-wool, having the narrow rim of metal thus firmly pressed against it, serves as an effectual filter of the air that passes in during cooling. But then it is essential that the heat be so equably distributed as to avoid heating any portion of the cotton to such a degree as to destroy its physical properties. The cotton-wool which you now see in the lid has been used for several experiments; yet you observe it is only slightly browned; it is not singed at any part, as it would have been unless the heat had been nearly uniform. This uniformity of the heat is provided for by having three shelves of sheet-iron (H H H) interposed between the large Bunsen's burner (I) and the bottom of the box, so as to prevent the heat from acting directly upon it; while at the same time the box is covered over with a cover of sheet-iron (KK), which reaches nearly to the ground, and, while it checks radiation, compels the heated air to travel over the whole exterior of the box and escape by holes at the top of the cover, whence it is conducted into a chimney by the tube (L). By these two means combined, the shelves below and the cover round about, we get the result which you see here. The cotton at the top of the box is browned to just the same degree as that at the bottom. Into such a box (about one foot in its three dimensions and furnished with a shelf in the middle) we may put a dozen sets of covered glasses such as I have described, together with their glass plates and shades. An aperture in the top of the box, well packed with cotton-wool, transmits the thermometer (M) to show when the temperature of 300° has been attained; and when this

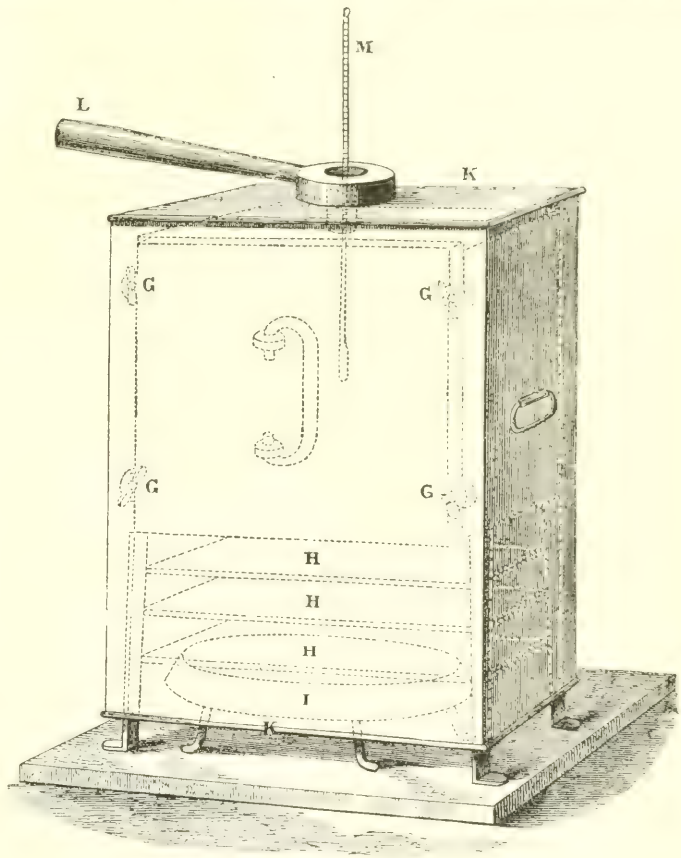


FIG. 3.

or any higher degree short of about 350° has been continued for two hours, the gas is turned off and cooling is allowed to take place ; and when the apparatus is quite cool, the covered glasses may be removed with confidence that they are perfectly free from living organisms.

In the next place, how shall any pure organic liquid be introduced into one of these purified liqueur-glasses without risk of contamination ? This we are now able to manage in a comparatively simple manner. The liquid is introduced by means of a flask of this form (N), having a bent spout, large at the commencement and comparatively narrow in its shorter terminal part (O) beyond the bend. The large size of the first part of the spout prevents it from ever acting like a syphon ; and the result is that, when liquid is poured from such a flask and the vessel is afterwards restored to the erect position, the end of the nozzle remains valved by a drop of the liquid ; and this guards the orifice, so that regurgitation of air can never take place through the nozzle. And the mouth of the flask being covered with pure cotton-wool (P), the air that enters the flask during the pouring out of the liquid is filtered of its dust by passing through the cotton. When the decantation is completed, a piece of rag wrung out of a strong watery solution of carbolic acid (1 to 20) is applied to the orifice of the nozzle, and, by capillary attraction, sucks out the drop ; after which a cap of carbolized cotton-wool (Z in Fig. 6, p. 360) is tied securely over the nozzle, the ligature obtaining a purchase upon the projection (O) upon the tube.[1] When this has been done, the liquid, if it was pure to start with, and the flask also pure, will remain

FIG. 4.

[1] Cotton-wool intended for a cap to cover the mouth or nozzle of a flask is conveniently applied between two pieces of open muslin, which ensure that the cotton shall remain as a uniform layer, and also permit it to be readily removed without leaving any of the cotton adhering to the glass. The best material for the ligature I have found to be very fine iron wire, tied firmly in a half knot, which is secured by giving the ends of the wire a bend, so as to convert them into hooks. A good mode of carbolizing the cotton-wool is to treat it with a solution of 1 part of carbolic acid in 100 parts of anhydrous sulphuric ether. The cotton greedily imbibes the liquid into all its parts and the ether evaporating leaves the carbolic acid behind in the cotton, which is thus rendered highly pungent and antiseptic.

ready to be used again in a pure condition a month or even a year later if required.

Now as to the means of preventing the entrance of dust into the liqueur-glass while it is being thus charged. Suppose I were going to charge this glass (Q) from this flask (the spout of which is alone given in Fig. 5), containing Pasteur's solution introduced on the 7th of August, yet you observe, remaining as pure and clear as when it was first prepared, although it has served for charging various liqueur-glasses. I should remove the cotton cap from the nozzle, and instantly slip the end of the nozzle into the opening which exists in the centre of this half of a substantial india-rubber ball (R), previously steeped in a strong watery solution of carbolic acid. The caoutchouc absorbs carbolic acid into its substance, so that, even though dry after such steeping, it is powerfully antiseptic. I then remove the shade and take off the glass cap, and immediately substitute the cap of india-rubber on the nozzle of the flask (as shown in the sketch). Fluid is now poured in, the flexible caoutchouc acting as a hinge during the movements of the flask, while the antiseptic cap excludes all living organisms ; and the instant the flask is withdrawn the glass cap is replaced and the shade put on. The hemispherical form of the cap also prevents lateral currents of air from depositing dust on the drop at the nozzle while it is being moved from one glass to another, and a second, a third, or a dozen glasses may be thus charged in succession ; and experience shows that this mode of procedure is so secure that the liquid will remain uncontaminated in such a series of vessels until it dries up through atmospheric influence.

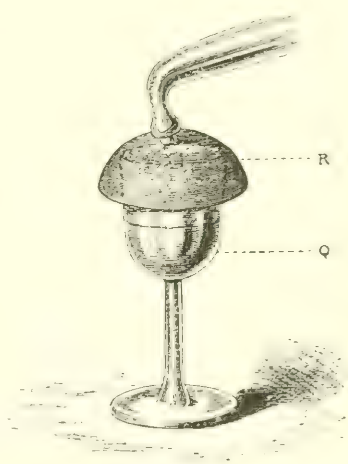


FIG. 5.

The last point is, How do we get the flask in a pure state with a pure liquid in it ? The flask itself is purified together with its caps of cotton-wool over the mouth and nozzle by being heated in the hot box. And here we have another great advantage arising from the uniform temperature of the box sufficient to purify cotton without impairing its physical properties. We have, therefore, a simple means of securing a pure flask to begin with.

Next, we wish to introduce into it a pure liquid. There is one organic fluid, peculiarly adapted for experiments on this subject, which can be got in the pure state with very little difficulty, and that is unboiled urine, provided we have a healthy urethra to deal with and a healthy bladder. All we have to do is to wash the surface of the glans penis thoroughly with a watery solution of carbolic acid, 1 to 40, in which strength it may be applied to the lips of the meatus urinarius without causing inconvenient smarting, and having thus merely purified the external integument, remove the cotton cap from the orifice of the flask and at once apply it to the organ and direct the patient to micturate. The purified glans takes the place of the caoutchouc cap, and as the urine enters no regurgitation of air is possible. As soon as the act of micturition is completed, a freshly carbolized cotton cap is tied over the mouth of the flask, and as surely as this process is properly performed, will you have the unboiled urine, together with its vesical mucus (which used to be regarded as the special ferment of urine), remain for any length of time free from development of bacteria or any other organism, and that whether the urine be acid or neutral in reaction.[1]

But suppose we have to deal with a liquid contaminated with organisms, like milk obtained from a dairy, we must purify it by heat. For this purpose I have always found exposure for an hour to a temperature of about 210° Fahr. sufficient.[2]

I say 210°, not 212°, which is the boiling-point of water, because the way in which we have proceeded is, after introducing the liquid into the purified flask, to immerse the vessel, to a higher level than that of the contained liquid, in boiling water: and, in consequence of a certain degree of evaporation which takes place through the cotton caps which cover the mouth and nozzle of the flask, the temperature of the liquid is prevented from ever rising fully to the boiling-point. We thus avoid the occurrence of ebullition; and this is a very great advantage, as we get rid of frothing; and, as already stated, the tem-

[1] For further details on this subject, see *Transactions of the Royal Society of Edinburgh*, vol. xxvii, 1875, pp. 315 et seq. (p. 275 of this volume).

[2] In making this statement I proceeded upon a pretty extensive experience with various liquids, such as water, Pasteur's solution, and turnip infusion, as well as milk. In my experiments with the last-named liquid, I had obtained it fresh from the cow milked directly into a glass vessel purified with carbolic lotion and then rinsed with water, and having filtered it through a fine cloth, exposed it to heat with as little delay as possible. But between the time of the meeting of the Society and that of going to press, I have found that milk which has been kept for some hours cannot be purified so easily. This I am inclined to attribute to the fact that milk, unlike the other liquids referred to, is a heterogeneous fluid containing oily particles in suspension, which tend as time passes to aggregate and coalesce. And it is quite conceivable that bacteria enclosed in such oily masses may be protected by them from the action of the hot watery liquid, the drops of butter acting as small portions of cheese have been found to do by some other observers. For it is a well-established fact that bacteria withstand a much higher temperature in the dry state than when acted on directly by hot water. I have also seen reason to believe that large numbers of bacteria grouped in masses are more resisting to the action of heat than isolated bacteria, as if the circumferential members of such a mass protected the central ones, and this circumference may perhaps aid in explaining the point in question. Again, if we consider the adventitious particles introduced in the form of dirt from the milkman's hands, &c., we cannot be surprised that difficulty should be experienced even with fresh milk, unless special precautions are taken to promote cleanliness.

perature which is attained proves adequate for the destruction of organisms in the liquid. All we have to do then, supposing the interior of the flask perfectly pure, is to introduce the liquid into the lower part of the flask with a view to immersion in a saucepan of boiling water: but then the most scrupulous care must be taken that no portion of the liquid so introduced shall come into contact with the upper parts of the interior of the flask; for any particles deposited there would fail to be acted on by the full heat of the water in the saucepan. Now the mode in which I filled the flasks in my earlier experiments was this. Having provided myself with a rag soaked with a strong solution of carbolic acid (1 to 20), I washed with it the exterior of a long funnel, and, wrapping the rag round the lower end of the funnel in sufficient mass to cover the mouth of the flask, I substituted the mass of antiseptic material for the cotton cap with which the mouth was previously covered, pushed down the funnel through the rag, poured in the liquid and withdrew the funnel, taking good care that the drop at its extremity did not touch the interior of the flask. A freshly prepared carbolized cotton cap was then applied to the mouth of the flask at the moment of withdrawal of the antiseptic rag, and the flask was immersed in the saucepan.[1]

If I proceeded in this way with Pasteur's solution or with turnip infusion, I always had success; but when I did the same thing with milk, time after time, to my great disappointment, I failed altogether. What was the explanation of the failure? Some persons might have said, 'Oh! the explanation is very easy to find. There are in milk complex organic molecules which, though as yet mere chemical substances, are, we imagine, ready to develop into living beings, and it is this complex constitution of the milk that makes you fail; whereas, your Pasteur's solution is a comparatively simple material, and turnip infusion may, for aught you know, have its molecules more simply constituted than milk.' I felt sure that this was not the true explanation, but that there must have been some defect in my method of procedure. It may perhaps have occurred to some of you what that defect was; it was this, that if we pour any liquid through a funnel, we invariably have air pass along with it. Air-bubbles consequently formed upon the surface of the liquid, and those bubbles bursting dispersed their dust in the air within the flask; so that it might well happen

[1] Means must be taken to prevent the flask from being floated up by the water in which it is immersed. This I have done by tying the flask into a vessel, such as a soap dish, containing shot. The flask so weighted is placed in the empty saucepan, warm water is poured in to a level considerably above that of the liquid in the flask, and brought to boil as quickly as possible and kept simmering for an hour. A piece of thin macintosh cloth, cut so as to adapt itself to the flask and cover the top of the saucepan, has the double advantage of preventing the water from boiling quickly away and avoiding moistening of the cotton about the flask by drops of condensed vapour.

that such particles, including perhaps some atmospheric organisms, might be deposited upon the upper part of the vessel, and so fail to be destroyed when the liquid was heated. But why should success be more likely with Pasteur's solution than with milk? Simply for this reason, that milk is a material which serves as a pabulum for almost all organisms. I once met with a bacterium, but only once, that would not live in milk; for extremely numerous as the varieties of bacteria appear to be, almost all of them seem to thrive in that liquid, whereas it is a common thing to find bacteria which, if put alive into Pasteur's solution, will not grow in it at all. The defect in our method having been discovered, there was no great difficulty in correcting it. It was done by substituting for the funnel this syphon (see Fig. 6), consisting of two glass tubes (S and T) connected by a tube of india-rubber (U), with a stopcock (V) in the course of the caoutchouc tubing. The syphon is first completely filled with water, the temperature of which should be higher than that of the air, so that there may be no dissolved air given off to form bubbles. Then suppose this (W) to be the fluid that we wish to introduce into the flask (X). We pass one leg of the syphon into it; then turn the tap and permit a sufficient amount of fluid to flow out to ensure that all the water has escaped from the syphon; then turn off the stopcock and proceed in the manner already described for the funnel. The tube (T) having been washed with strong carbolic lotion, carbolized rag is wrapped round its lower extremity, and this is applied to the mouth of the flask as the cotton cap is removed; the tube (T) is pushed steadily down to the bottom of the flask through the carbolized rag (Y), the stopcock is turned on and the liquid passes into the flask without the smallest air-bubble accom-

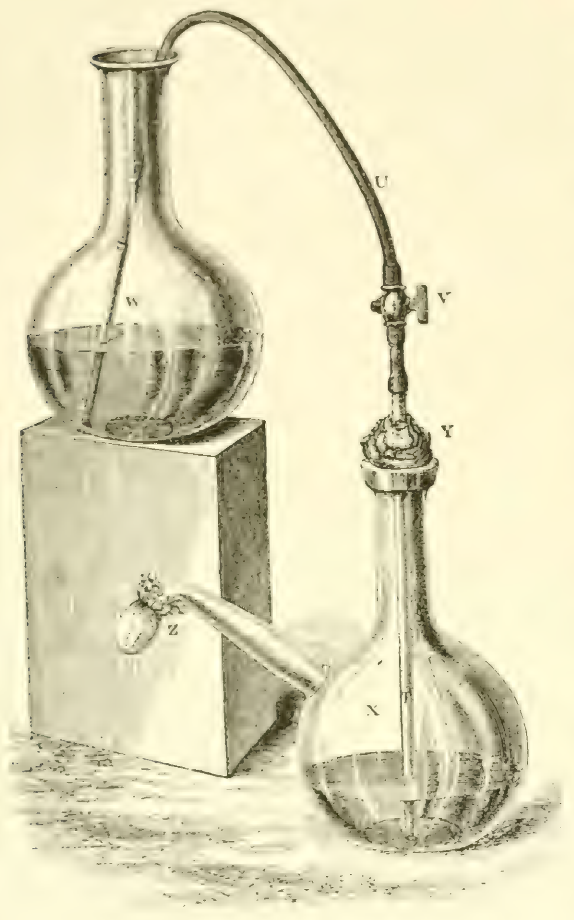


FIG. 6.

panying it. When a sufficient quantity has been introduced, the tap is again turned off, and the syphon is withdrawn through the antiseptic rag, and a fresh cap of carbolized cotton is tied over the mouth of the flask when the rag is withdrawn.

I have said that before I saw my mistake in using the funnel, I never succeeded with milk. Since I have adopted the syphon I have charged many flasks and never failed. Here is a flask of boiled milk (or rather of milk that has been exposed to a temperature of 210°) prepared on the 7th of August, and remaining we may safely say as pure as it was then. You observe it is still perfectly liquid and unaltered in appearance. Now I venture to remark that this failure and correction of the failure are extremely instructive, as showing how the development of organisms under circumstances in which we cannot at first explain their occurrence may be really due to fault on our part, defect in our own manipulation.

So much for our method of procedure. I will now go on with the main subject of this communication. I selected the lactic fermentation as one peculiarly favourable for investigation : first, because the effects which it produces in milk are extremely striking and readily recognized—the solidification which takes place being obvious at a glance, and the souring as shown by test paper being also a very conspicuous change ; and in the second place because the ferment which occasions these alterations is, in ordinary localities, a very rare ferment ; and if it be rare, it is not likely that any defects in our manipulations will lead to its accidental introduction.

It may seem strange that the ferment that leads to the souring of milk should be rare, but such is the fact ; in dairies it appears to be universal, but in the world at large it is scarce. If you charge a series of pure liqueur-glasses with boiled milk and take off their caps so as to expose them to the air for about half an hour each, doing this for the various glasses at different times of the day or in different rooms, you will be sure to have organisms develop in all of them, of the nature of filamentous fungi and bacteria ; and you will see fermentative changes ensue ; but, so far as my experience goes, you will not see the coagulation and souring of the lactic fermentation, nor will you find under the microscope the peculiar organism to which I have given the name of *Bacterium lactis*, which is represented here (Plate XIV, Fig. 9) as it occurs in ordinary curdled milk, and which may be seen under one of the microscopes on the table, in milk taken from the cow yesterday.

This organism is a motionless bacterium, that is to say, exhibiting no movement except a slight jogging, occurring most commonly in pairs, but frequently in chains of three, four, or more individuals, each segment being of somewhat rounded form, more or less oval, with the long diameter in the direction of the length of the chain, and often showing, on careful focusing, a line across their central part indicating transverse segmentation. They vary in diameter, as I shall have occasion to notice again, full-sized specimens measuring about 1-20,000th inch.[1] You always find them, as far as I know, in souring milk from a dairy, and a touch with the point of a needle which has been dipped into such souring milk will induce their development with great rapidity in a glass of boiled milk, together with the characteristic curdling and souring, showing that the boiled milk is thoroughly disposed to the lactic fermentation as soon as the appropriate ferment enters, while that ferment, as already stated, is not likely to occur as the result of exposure to the air of your study or any ordinary situation.

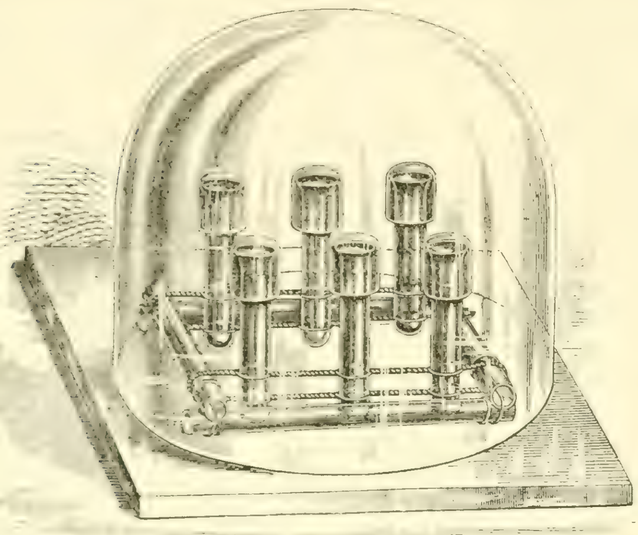


Fig. 7.

These little glasses (represented on a reduced scale in Fig. 7) illustrate the same point as regards unboiled milk. Each is a small test-tube provided with a cap made of the bottom of a larger test-tube, and arranged along with five others in a stand made of pieces of glass tubing and stout silver wire, and placed under a common glass shade on a plate of glass. Four such sets of glasses, making twenty-four glasses in all, were purified by heat in the hot box, together with their plates and shades. Another larger glass, provided with a glass cap, having been also purified by heat in the box, milk was drawn directly into it from a cow standing in a little orchard belonging to a dairy farm and within two yards of the dairy itself, the glass cap being removed immediately before the milking commenced, and reapplied as soon as the vessel was charged, the quantity amounting to about two ounces. Then by means of a syringe connected with a purified pipette the milk was at once transferred, in a room in the farm-house, to the little glasses, each cap being replaced as soon as the glass was charged. Yet in spite of the care that was taken, organisms must have

[1] In giving these as the characters of the *Bacterium lactis*, I do not wish to be understood as stating that this species can always be certainly recognized by its morphological features alone.

entered from the air of the orchard or of the apartment, possibly also from the cow's teat (though this had been previously washed by drawing milk from it just before the glass was charged); for you observe every one of the twenty-four glasses shows manifest evidence of alteration, and there can be no doubt that these changes are due to the development of organisms. No fewer than seven of them are seen, by aid of a pocket-lens, to contain filamentous fungi of various sorts, for aught I know undescribed, and certainly none of those commonly met with in milk.[1]

Two of the glasses containing filamentous fungi are represented of natural size in the sketches reproduced in Figs. 1 and 2, Plate XIV. The other glasses present appearances which members of the Society, if they will examine them, will find to be exceedingly peculiar. No two are alike: some have a golden-yellow aspect (Fig. 8), some a green tint (Fig. 7), while many are studded with brilliant red spots (Figs. 3, 4, 5 6) either alone or associated with other colours, and the lower parts of the contents of the several glasses are changed to various degrees of translucency and shades of tint, implying different fermentative changes. But there is no reason to suspect in any of them the occurrence of the *Bacterium lactis*, or the lactic fermentation. I have not had opportunity to examine the contents of these glasses microscopically, but in another experiment made in the same way a few days previously with twelve similar glasses I found, just as here, some affected with filamentous fungi, and the majority altered in various ways in colour, including definite specks of different shades of orange growing gradually as the red ones in this set did from a mere speck to larger and larger spots; and, examining with the microscope the contents of every one of those glasses, I found the orange specks to be composed of organisms in the form of little spherical granules peculiarly grouped, which I have elsewhere described under the name of Granuligera;[2] and other glasses, having alterations without such bright and definite colours, presented bacteria of different appearances, but in no case did I find the *Bacterium lactis*.

I also performed other experiments of a very simple character which illustrate equally well the rarity of the lactic ferment in the air, even though it be the air of a cow-house. The teat of the cow and the milkmaid's hands having been washed with strong watery solution of carbolic acid, milk was received directly into a purified flask of the kind above described (p. 356), and from this a dozen purified liqueur-glasses were charged in my study within about half an

[1] The filamentous fungi most frequently found in milk that is kept for a considerable period are the *Oidium lactis*, the common blue mould *Penicillium glaucum*, the common green mould of cheese, *Aspergillus glaucus*, and two forms of Mucor, the *M. mucedo* and *M. racemosus*.

[2] See *Transactions of the Royal Society of Edinburgh*, loc. cit., p. 319, and Plate (p. 275 and Plate VI of this volume).

hour. All these glasses underwent fermentations, and exhibited organisms under the microscope, but none showed the lactic fermentation or the *Bacterium lactis*.

With regard to the cause of the strange, perhaps unprecedented, appearances presented by the milk in the little glasses shown to the Society, the explanation undoubtedly is, not that organisms of a specially rare kind were here present, but that species, perhaps exceedingly frequent in other media, had an exceptional opportunity for coming forward in milk, in consequence of the exclusion of ferments such as the lactic, the butyric, &c., which, when present in milk, as they commonly are, take the precedence of others, and so alter the fluid as to render it an unsuitable pabulum for the multitude of other kinds.

Here I have another set of little test-tube glasses, twelve in number, with which the same experiment was repeated two days later, only with still more careful precautions against the entrance of organisms from the air or from the teat ; but even here, although the appearances are less conspicuous than those in the other twenty-four, a careful inspection shows that, in ten out of the twelve, organisms of one kind or another have entered, but two of them remained perfectly unchanged in aspect six weeks after the performance of the experiment, and on examining the milk from one of these I found it fluid, perfectly natural in reaction and in taste, and free from any organisms that could be discovered by the microscope. Thus was at length attained the object of these experiments with the little glasses, viz. the proof that unboiled milk, as coming from a healthy cow, like urine from a healthy bladder, really contains no material capable of giving rise to any fermentative change or to the development of any kind of organism which we have the means of discovering.

The lactic ferment is as scarce in ordinary water as we have seen it to be in the air. If I prepare a series of glasses of boiled milk in the way that has been described, and add to each a drop, say half a minim, of tap water, I find that fermentative changes, such as putrefactive or butyric alterations, occur in all, but that none exhibit the souring or curdling of dairy milk. An extremely instructive experiment is to inoculate each of a series, say ten, of such glasses with a very small drop of a constant size for all, which can be readily done by means of a syringe like this (Fig. 8), having a graduated nut (*a*), revolving on a fine screw on the piston rod (*b*), each degree on the nut corresponding to 1–100th minim, so that either 1–100th, or 1–50th, or 1–200th, if it be desired, can be expelled at pleasure.[1] Supposing 1–100th minim of water to be thus

[1] It is essential to the precise working of this apparatus that there be nothing elastic in its composition, otherwise drops of varying size will be furnished by it. Thus, an india-rubber junction between the syringe and the nozzle is inadmissible. The nozzle of glass tube (*c*) is screwed upon the body of the syringe by means of the brass adapter (*d*), to which the glass tube is secured with a cement which I have found very useful on account of its power of resistance to the action of boiling water, viz. finely powdered

introduced into each glass, the result will probably be that fermentative changes of totally different kinds will occur in the various glasses, as indicated by striking differences of colour in the contained milk and differences of odour in the air in the glass shades; and, what is extremely interesting, some glasses will escape all change. This last fact proves at once the important truth that the fermentative agency in water, the existence of which was pointed out long ago by Dr. Burdon-Sanderson, is not matter dissolved in the water, but consists of insoluble particles of some kind or other suspended in it. For if the ferment were dissolved in the water, every equal-sized drop would produce an equal effect. But the fact is, as already stated, that when drops of such minuteness are employed, some of the inoculated glasses escape altogether, and those which are affected exhibit different kinds of fermentation, and we thus learn from this simple experiment not only the truth that the fermentative material is in the form of insoluble particles, but that every minim of ordinary water contains several different kinds of ferments, which, though generally confused through being mixed up together, declare their individual peculiarities when isolated by this method of separation.

These various fermentative changes were invariably found associated with bacteria, those in different glasses sometimes showing themselves conspicuously different under the microscope, though often only distinguished by their effects. Thus, in one case, the cream being particularly thick, a bright vermilion-coloured point appeared after some

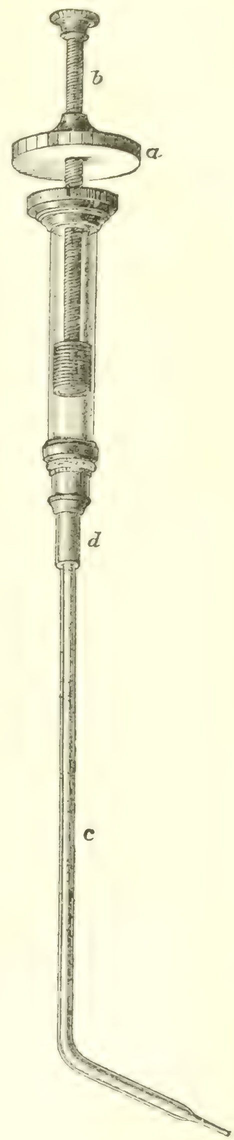


FIG. 8.

gum copal brought to a liquid state by a high temperature and then applied to the objects to be cemented, which have previously been heated to an equally high degree. The presence of an air-bubble in the water within the syringe would also by its elasticity vitiate accuracy of performance. This is got rid of, so far as the body of the syringe is concerned, by first accurately charging it with water that has been boiled to dispel its dissolved air. The water of inoculation, with which the glass nozzle is to be filled, is also raised to a somewhat higher temperature than the air of the apartment by placing the vessel containing it before the fire for a few minutes. The nozzle with its adapter is purified by boiling it in water in a saucepan for about half an hour, after which its fine end is immersed in the water for inoculation, and when it is filled beyond the bend the other end is depressed, so that the rest of the filling may be done by syphon action. When a drop of water projects from the adapter, it is applied to a correspondingly projecting drop of water at the mouth of the syringe, and the two drops coalescing prevent the introduction of a particle of air when the nozzle is screwed on. With these precautions drops of exactly the same size can be ensured.

days at the spot of inoculation, and gradually spread over the surface, and on examining with the microscope a portion taken with a purified needle from the vermilion spot, I found it teeming with bacteria, while a portion of the uncoloured cream in the vicinity showed nothing but the usual milk globules. Here then was a remarkable change going on in the milk *pari passu* with the development of bacteria, and doubtless occasioned by them, yet the bacteria themselves were of ordinary double-rod form and of about medium size.[1] But various as were the changes produced in the milk by inoculation with water, there was no instance in the course of several such experiments of the lactic fermentation resulting from it. We see, therefore, from the facts which I have adduced, that the souring of milk, instead of being—as might naturally be supposed *a priori* from seeing it occur constantly in all milk brought from a dairy—an inherent property of the liquid, is a change which, whether in boiled milk or unboiled, requires the introduction of something from without, and that something a scarce article, both in air and in water, except in dairies. Indeed, even in a dairy, though it exists in all the milk in the pans, it does not necessarily follow that it is the most frequent ferment in the air. I once took a glass of pure boiled milk to a dairy, and putting it down near one of the pans, removed its glass shade and glass cap, and left it exposed for a quarter of an hour, thinking it probable that the lactic fermentation would result. But it so happened that this was not the case. As a consequence of this exposure a filamentous fungus made its appearance in the milk, and also a bacterium, but a bacterium associated with a most extraordinary alteration, viz. viscidity in an extreme degree, reminding me of that of the glutinous drops that bead the spider's web. On introducing a needle into the top of the liquid, and raising it, I drew out a barely visible thread, which was a yard and two inches long before it broke. Such was the special fermentation that resulted from exposure to the air on that occasion even in a dairy; it so happened that, if any particles of the lactic ferment were floating in the air at all, none fell into the glass.

This particular fermentation, therefore, from the conspicuousness of its effects and the rarity of the ferment under ordinary circumstances, seemed a peculiarly favourable one for investigation.

And now, before proceeding further, I desire to correct a mistake into which I fell when investigating this same fermentation some years ago; for, next to the promulgation of new truth, the best thing, I conceive, that a man can do, is the recantation of published error. In the year 1873, I gave, in the

[1] These experiments were performed in the early part of the year 1875, and were briefly alluded to in a paper in the *Lancet* of that year (see *Lancet*, April 3, 1875, p. 470). Reprinted in vol. ii, p. 226.

Microscopical Journal, an account of the behaviour, as I supposed, of the *Bacterium lactis* in different liquids.[1] I stated that, having obtained souring milk from a dairy, I inoculated a glass of uncontaminated unboiled urine with a small drop, and the result was the development in that liquid of organisms with a very different appearance from the bacteria which I had seen in the souring milk. The latter had the characters of *Bacterium lactis*, as already described (Plate XIV, Fig. 9), viz. pairs or chains of small oval bodies, with lines of transverse segmentation. Those in the urine, on the other hand, were broad and extremely long, often coiled up like a spirillum, though motionless, like the *Bacterium lactis*. There were, however, what certainly looked like transitional forms between the two. From this urine I inoculated another glass of the same liquid, the result being a reproduction of the same large spirillum-like organism. I next inoculated from the second urine-glass one of Pasteur's solution ; and now obtained appearances different from any before seen, viz. instead of either the motionless chains of *Bacterium lactis* of the milk, or the spirillum of the urine, an actively moving minute double bacterium. But on introducing a small drop of the Pasteur's solution so peopled into a third urine-glass, I got back large coiled organisms resembling those of the former glasses of the same fluid, except that these exhibited languid motion. Yet the introduction of a small drop from this third urine-glass into one of pure boiled milk was followed by souring and curdling just as if the inoculation had been made with sour milk from the dairy. The apparently transitional forms in the first urine-glass made me suppose that the spirillum was the *Bacterium lactis*, modified by its new habitat. I also examined in a cultivating glass, under the microscope, a drop of a mixture of fresh urine with a small quantity of the Pasteur's solution containing the moving bacteria, and found that the minute active organisms first seen gave place to larger languidly moving specimens, and thus I thought I had evidence of a transition from one to the other. And lastly the efficiency of the contents of the third urine-glass as a lactic ferment, in spite of the various forms assumed in the various media, confirmed my belief that I was observing one and the same organism in all the glasses. And if this was really the case, considering how thoroughly the organism must have been washed in the various media of all chemical material that might be supposed to be originally associated with it in the milk—particularly considering that the lactic fermentation does not occur at all in either urine or Pasteur's solution—the chain of facts appeared a strong confirmation of the view that this particular bacterium was really the cause of the lactic fermentation. I was mentioning these facts a few months ago to an eminent physiologist, who took the view that after all bacteria might

[1] See *Quarterly Journal of Microscopical Science*, October 1873 (p. 309 of this volume).

be mere accidental concomitants of the fermentative changes ; and when I had finished my story he said, 'Well, I am convinced.' I thought to myself, 'If I have convinced this eminent teacher by these facts, they are worth proving more rigorously ; I shall have a little time between giving up my surgeoncy in Edinburgh and going to London, and I will devote it to repeating the experiments ; but this time I will make continuous observations under the microscope, and trace, if I can, the actual process of transformation of the organism from one form to another.' Accordingly, I got some souring milk from the same dairy as before, and proceeded, in the first place, to inoculate from it a glass of uncontaminated unboiled urine, and also a glass of pure Pasteur's solution. The result in the case of the urine was that, instead of getting a large motionless spirillum as in the corresponding experiment of four years previously, I found an active double bacterium of moderate dimensions. In the Pasteur's solution, on the other hand, instead of the minute very actively moving bacterium of my former experience, I obtained only motionless bacteria of various dimensions.

Here then were the facts all wrong. What was the explanation ? I had obviously got some accidental contamination of the *Bacterium lactis* with other forms, although in doing the inoculations I had only introduced a very minute portion with the point of a heated needle. So I determined to try if possible to get rid of concomitant bacteria of other kinds, and the way which occurred to me as a possible mode of doing this was to dilute the souring milk with so large a quantity of boiled and therefore pure water as to have on the average, so far as it could be estimated, only one bacterium of any kind to every one of the drops with which a set of glasses of boiled milk should be inoculated. If this could really be done, as the *Bacterium lactis* was certainly in much larger numbers than any other kind, I might hope that some at least of the drops of inoculation might contain it isolated from other species, and that thus I might have the *Bacterium lactis* develop pure and unmixed in the inoculated milk. Accordingly having obtained some souring milk from the dairy, I inoculated a glass of boiled milk from it by dipping the point of a heated needle successively in the two liquids, and when the odour of souring milk was perceptible in the air under the glass shade, I found bacteria present on microscopic examination, and endeavoured to estimate their numbers in proportion to the liquid.

This was done in the following manner. By means of the syringe already described (p. 364) one or more hundredths of a minim could be measured with precise accuracy ; and I found that 1–50th minim exactly occupied a circular plate of thin covering glass, half an inch in diameter, so that when such a drop was placed on a glass slide, and a covering glass of the size mentioned and quite flat was put down upon it, all air was expelled from under the latter, and the rim of fluid that formed round about its margin was so narrow as not to measure a quarter of the diameter of the field of the microscope even when the highest magnifying power was used. In other words, 1–50th minim was disposed in a thin uniform layer of the exact size of the covering glass. Hence the number of bacteria under the glass slip, that is to say in 1–50th minim, was equal to the number of the bacteria in a field of the microscope multiplied by the number of times the area of that field went into the area of the covering glass. The micrometer gave the diameter of the field in thousandths of an inch ; and the covering glass measured 500-thousandths of an inch across : and the areas of the circles were of course proportioned to the squares of those diameters. All that was needful, therefore, in order to enable me to calculate the number of bacteria in 1–50th minim, was to form a fair estimate of the number of bacteria per field, and this was done by counting the organisms in a considerable number of fields and taking the average.[1]

It so happened that two kinds of bacteria were seen under the microscope, one motionless, with the characters of *Bacterium lactis*, the other much less numerous, with longer segments and in active movement. As a rule, on examining milk which is undergoing the lactic fermentation but is still fluid, the *Bacterium lactis* is alone discoverable ; but in this instance we had ocular proof of the admixture of another sort, though in much smaller numbers. As the result of the estimate which I made of the number of bacteria present in every 1–50th minim, I found it necessary to dilute the milk with no less than a million parts of boiled water in order that every 1–100th minim should contain on the average a single bacterium.[2] This having been done, 1–100th minim of the

[1] I found great advantage from placing the circular covering glass (with the liquid) on the under surface of a plate of thin glass, large enough to cover a chamber excavated in a thick glass plate. A drop of water sufficed to fix the edges of the thin plate of glass down upon the thick, and served also to prevent any evaporation taking place from the liquid to be examined into the air-chamber, so that the liquid was maintained of constant quantity. At the same time, the object being on the under side of the thin plate of glass, an immersion lens could be used for examining it to its extreme limits without the inconvenience of the liability of the drop of water under the object glass mingling with the liquid examined, as would have been the case had the object been on the upper side of the glass plate.

[2] The dilution with this enormous proportion of water was readily done by dividing the process into two stages. First, by means of the small syringe (figured at p. 365) with purified nozzle, 1–100th minim of the milk was added to 200 minims of boiled water, which had been measured into a purified glass by means of a pure graduated pipette connected with a syringe, the end of the pipette adapted to the syringe, having been stuffed with cotton-wool before purification in the hot box, so as to filter air that passed into the pipette from the syringe. When the milk had become thoroughly diffused through the water, as indicated by uniform opalescence (the diffusion having been promoted by stirring rapidly with a pure glass rod), a minim of this first dilution was transferred by means of another and smaller pure syringe-pipette into a second purified glass, which had been charged with 50 minims of boiled water. I need hardly add that the utmost care was used to avoid more than momentary exposure of the liquids manipulated, and of the purified pipettes or other apparatus employed.

infected water was added by means of the small syringe [1] (figured at p. 365) to each of five glasses of pure boiled milk. The result of this inoculation was that one only of the five glasses was affected at all. The contents of four remained permanently fluid and unchanged, and when examined with the microscope after the lapse of thirteen days, showed no bacteria of any kind. The milk of the fifth glass, however, was, in the course of the third day after inoculation, converted into a solid mass, and on examination was found to be sharply acid, and under the microscope there were seen among the granular masses of caseine countless motionless bacteria with the ordinary characters of *Bacterium lactis*, specimens of which were sketched and are reproduced in this diagram (Plate XIV, Fig. 9). No other bacteria, however, were to be discovered; we had got rid of the moving species which was seen to be associated with it in the milk before dilution, and *a fortiori* it might be believed that other species, doubtless present in the original milk, but in too small numbers to be detected, had been avoided.

Having therefore presumably obtained the *Bacterium lactis* pure and unmixed, I proceeded to ascertain its behaviour in other media. I inoculated a glass of uncontaminated unboiled urine with it; and now, instead of either the moving bacterium which resulted from a corresponding inoculation with sour milk a few days before, or the large coiled organism of the experiments done four years previously, there appeared a motionless bacterium with identically similar characters to those of the *Bacterium lactis* in the glass of milk, as will be seen from this diagram (Plate XIV, Fig. 10) made from a sketch taken two days after inoculation of the urine. Had either of the forms seen in the previous experiments been present, the insignificant motionless *Bacterium lactis* would probably have escaped notice altogether. In the course of the first twenty-four hours its growth was indicated by delicate white vertical streaks on the glass without any turbidity of the liquid. Next day, however, the fluid was decidedly nebulous, but after that period the growth was exceedingly slow, and very little effect was produced upon the urine as regards either odour or reaction. Nevertheless it still retained its power of acting as a lactic ferment when introduced into milk even after four days' residence in the urine; for having inoculated at this period eight glasses of boiled milk with drops of the urine diluted with enough boiled water to provide about three bacteria on the average to each drop, all the glasses soured and curdled within three days.[2]

On the day on which this fact was observed, and when the bacterium was

[1] The nozzle of this syringe was purified by boiling it in water in the interval between its employment referred to in the above note and the inoculation of the milk-glasses.

[2] Even after seventeen days in the urine the organism still retained the power of causing lactic fermentation, though it was then not quite so energetic, requiring an additional day to produce curdling.

therefore still in full activity, I introduced a small portion of the curd from one of the glasses into a glass of Pasteur's solution, in order to study the behaviour of the organism in that fluid. In this experiment I made use of what I have called a ' separation-tube ', a piece of glass tube bent at an angle of about 45° (see Fig. 9), with one leg shorter than the other, the shorter leg closely packed with moist cotton-wool (*c*), which is purified together with the tube by boiling in water. The apparatus is then transferred to a pure liqueur-glass, in which it is arranged with the longer leg (*f*) placed vertically and kept in this position by a mounting of silver wire (*g*) applied to the tube before its purification. The liquid to be experimented on is now poured into the glass to a higher level than the mouth of the shorter leg of the separation tube, but not so high by a considerable interval as the top of the longer leg. The liquid finds its way slowly through the cotton and rises in the longer leg, and it is into the liquid in the longer leg of the separation tube that the material of inoculation is introduced. The cotton in the shorter leg is so closely rammed that it serves as an effectual filter to prevent the passage of any particles of ordinary solid matter ; but if any organism capable of developing in the liquid is introduced into the longer leg, it will work its way through the cotton, and show itself in the general liquid in the glass. Even a motionless bacterium or a filamentous fungus will traverse the closely packed mass, at a rate corresponding with the rapidity of its development. Thus we have a simple means of separating things which are living and capable of developing in any particular liquid from particles which are not alive, or which, though living, are incapable of growing in that medium. It was into the longer leg of such a separation-tube in a glass of Pasteur's solution that I introduced the morsel of curdled milk containing the actively growing *Bacterium lactis.* For a long time it appeared as if no growth whatever of the organism had taken place in its new habitat. But when nearly three weeks had elapsed, thinking that the little bit of curd looked somewhat swollen, I subjected it to microscopic examination, and found that the substance of the curd seemed to have disappeared, its place being occupied by small bacteria having the characters of *Bacterium lactis,* showing that the organism really had undergone some development. But it seemed to have grown only where it had the material of the curd to feed upon ; for the outside liquid in the glass showed no trace of any organism either to the naked eye or under the microscope. Thus it appears that the *Bacterium lactis,* though not destroyed

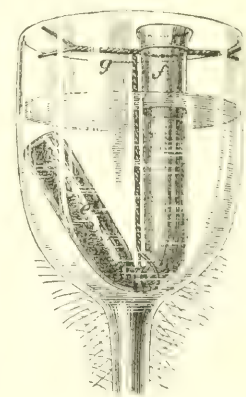


FIG. 9.

by Pasteur's solution, does not find in that fluid the materials requisite for its nutrition. I also imitated in another glass of Pasteur's solution the experiment of four years before, by inoculating it with urine in which the *Bacterium lactis* was developing actively, but here again, although the specimen was kept twenty-one days, no sign whatever of bacteric growth appeared. It was therefore plain that the *Bacterium lactis* is really incapable of growing in pure Pasteur's solution.[1]

Thus I was forced to the conclusion that the appearances which I had described in my former communication as due to modifications of the *Bacterium lactis* in urine and Pasteur's solution had been entirely deceptive, and had been occasioned by the accidental accompaniment of other species. And now that we know from the results of experiments like those with the little test-tube glasses how very numerous are the bacteria and other organisms which really infest milk, it is easy to understand how such a confusion may have arisen.[2]

Now, however, having good reason to believe that I had got the *Bacterium lactis* pure and unmixed, I proceeded to perform the experiment which constitutes the most important feature of this investigation. I have already described the mode of procedure when speaking of the means adopted for isolating the *Bacterium lactis.* Its object now was to obtain, if possible, absolute proof, which would commend itself to the judgement of all, that the *Bacterium lactis* is really the cause of the lactic fermentation, and no mere accidental concomitant of the change.

[1] It is right that I should state that the solution which I employed differed from that made according to Pasteur's formula, in having only half the proportion of sugar, and in having its mineral salts derived from wood ashes instead of from the ashes of yeast. It was, however, with solution of precisely the same composition that I had worked in the experiments of four years previously.

[2] It is not, indeed, altogether easy to see what the precise train of events may have been in the experiments of four years ago. I may suggest the following as possible. First, along with the *Bacterium lactis* with which the first urine-glass was inoculated (see p. 367), was accidentally introduced another kind of bacterium, which produced the large spirillum-like appearances. This adventitious organism grew freely in the urine, along with the slowly growing and inconspicuous *Bacterium lactis.* It presented considerable varieties of form, some of them closely resembling chains of *Bacterium lactis*, but it was in reality a totally distinct species. Then when the Pasteur's solution was inoculated from the urine, both organisms were again introduced together. Here the spirillum-like organism underwent a modification, assuming the characters of an actively moving double bacterium, a transition which was, I think, sufficiently traced under the microscope (see *Microscopical Journal*, loc. cit.). Meanwhile, the *Bacterium lactis* lay dormant in this medium, but retained its vitality, and by accident it happened that one or more of these still living individuals, lying perhaps at the surface of the liquid in the speck of scum that commonly results from inoculation, was transferred along with the other organism to the last urine-glass. Here the latter resumed the spirillum-like form which it had before shown in urine, though retaining now for a while in a limited degree the movement it had acquired in Pasteur's solution. The individual or individuals of the *Bacterium lactis* introduced into the urine along with it were here able to develop again, though slowly, and some of their progeny entered the glass of boiled milk inoculated from this urine-glass, and in that medium developed with their accustomed rapidity and with the usual fermentative effect. It may, perhaps, seem trivial to record this complicated hypothetical explanation, but I am induced to do so for the sake of illustrating the excessive care required in order to avoid deception when we are dealing with such extremely minute organisms.

On the 30th of August last, having provided sixteen pure glasses of boiled milk, and having estimated, in the manner already described, the number of bacteria present in every 1–50th minim of a glass of boiled milk which had been inoculated the day before by touching it with a heated needle dipped in milk curdled under the influence of the pure ferment, I diluted a drop of this milk with boiled water to the requisite degree, and introduced into each of ten of the sixteen uncontaminated glasses a drop calculated to contain on the average a single bacterium, while five of the rest received each a drop supposed to contain two of the organisms, and the remaining glass was inoculated with a quantity in which, according to the estimate, there would be four bacteria. The result was that within three and a half days the glass into which four bacteria were supposed to have been introduced contained a curdled mass, and the five which had received the drops arranged for two bacteria each had all undergone a similar change. Of the ten inoculated with drops averaging one bacterium each, the majority were at this period still fluid ; but some assumed the solid condition in the course of the next twenty-four hours, though at different times. But of this series of ten exactly five, as it so happened, remained permanently fluid.

This was just the sort of occurrence which might have been anticipated if we believed the bacteria to be really the cause of the fermentative change, and supposed that we had succeeded in forming a fair estimate of their numbers. It was to be expected that the bacteria would not be distributed with perfect uniformity in the water with which the milk was diluted ; and hence, of the drops containing on the average one bacterium each, some would probably be destitute of the organisms, and the rest have more than one, and in differing numbers, involving slight differences of time in arriving at the stage of the fermentative process which induced coagulation.

But not only were the results of this experiment in harmony with the view that the *Bacterium lactis* was the real fermentative agent : they would, as I believed, afford indisputable evidence of the truth of the theory, provided it should turn out, as former experience made me feel sure would be the case, that every glass which had curdled contained the bacterium, and that every one which remained fluid contained none. Though, as I have said, I did not doubt that this was the state of the case, yet I went through the laborious process of examining the contents of all the sixteen glasses just before leaving Edinburgh, nine days after the time of the inoculation. All those which had coagulated still contained an unaltered white curd with a glistening upper surface, and nothing to indicate the supervention of any change secondary to that of the lactic fermentation. The air in the glass shade of each had the odour of souring, the taste of a little portion of the curd removed for investigation was sour and its reaction sharply acid, and under the microscope, in every instance, bacteria with the characters of *Bacterium lactis* were found, but no other organism. And in the case of the remaining five glasses, where the milk was still fluid and unchanged in appearance, the air in the glass shade had merely the slight odour of suet, which Pasteur long since pointed out as resulting from oxidation; the taste was that of fresh milk, and the reaction showed the peculiar form of neutrality which fresh milk exhibits, both blue and red litmus paper acquiring an intermediate purple tint.[1] And on subjecting the contents of each to microscopic examination, I could discover under a protracted search no organisms of any kind. I have brought before the Society one of these last glasses (still under the protection of its glass cap and shade) to show that even after the lapse of nearly four months the milk remains fluid and unaltered. I need hardly say that it required considerable care to bring these glasses from Edinburgh without having their contents spilled. Nevertheless this is one which was successfully transported; and I have placed under one of the microscopes a drop of its milk, in which it will be seen that there are no organisms present, and that the only alteration discoverable is that some of the milk globules have assumed an angular form as the result of evaporation.

Here, again, is one of the glasses which underwent the lactic fermentation, and its appearance is in truth as remarkable as that of the other. We know that if curdled milk is kept under ordinary circumstances it soon loses its original characters. The *Oidium lactis* grows upon its surface, the *Penicillium glaucum* or some other common mould probably shows itself, and the curd acquires first a cheesy and then a putrid smell, accompanied with great alterations of its aspect. Here, however, the lactic fermentation having occurred single and alone, we have a pure white curd to this hour, as if the milk had curdled yesterday, and any little smell which there is in the air of the glass shade is a slight sour odour.[2]

[1] Neutral urine presents this same reaction.

[2] For the sake of any one desiring to repeat this experiment, it may be well for me to add a few matters of important detail. The estimate of the number of bacteria present in the milk should be made within about twenty-four hours of the inoculation of the glass with a purified needle-point dipped into milk souring with the pure ferment, and then applied to the milk which is to be inoculated, close to the edge of the glass, as distinguished from the central part, from which the drop will be afterwards taken. At ordinary temperatures the bacteria will then be found about the period referred to of full size and isolated, and therefore easily counted; whereas if too long a time is allowed to pass after inoculation, they will be found too numerous to be easily counted, and often of small size and in groups composed of an indefinite number. Further, if the bacteria are counted in one drop of the milk, and another drop is taken for dilution and inoculation, two great inconveniences will result. First, there will be no security that the two drops contained the same proportions of bacteria; and, in the second place, the knowledge that the bacteria are in process of multiplication with great speed (doubling their numbers in about an hour) leads to most undesirable hurry in the microscopic examination and the subsequent

And now let me dwell for a few minutes on the inference to be drawn from these facts. We have seen that boiled water rendered infective by the admixture of a small quantity of milk undergoing the lactic fermentation, having been introduced in drops of equal size into ten glasses of pure boiled milk, five of those glasses underwent the lactic fermentation, characterized by souring and curdling, while five remained altogether unaffected. This proves that the same truth holds regarding the lactic ferment which we have before established with respect to the various ferments that occur in ordinary water, viz. that it is not a material soluble in water, but consists of insoluble particles. For had it been dissolved in the water of inoculation, every equal-sized inoculating drop would have produced the same fermentative effect. Next we have to consider the bearing of our facts on the nature of those insoluble particles, the question being whether they were the bacteria or consisted of some so-called chemical ferment destitute of life, of which the bacteria were a mere accidental concomitant. Let us assume, for the sake of argument, that it is possible for insoluble particles to exist devoid of vitality, yet capable of multiplying like the bacteria. Such a notion is unsupported, I believe, by a tittle of scientific evidence ; but, for the sake of argument, let us for a moment assume it. We should then be further obliged to suppose, in order to account for our facts, that these hypothetical particles, though merely accidental accompaniments of the bacteria, were present in precisely the same numbers, a thing which is utterly inconceivable. But we should have to go further and suppose, what is equally inconceivable, that these bodies of different natures, though mere accidental concomitants were not only exactly equally numerous, but invariably accompanied each other in pairs ; so that when a bacterium was introduced into one of the glasses, it was always associated with a particle of the hypothetical true ferment, and whenever the bacterium was excluded, the hypothetical ferment likewise failed to enter. Hence, as the only other possible interpretation of our facts involves what is utterly inconceivable, I venture to think that those facts will be admitted

calculation, besides leaving uncertainty as to the estimate, in consequence of the development that is proceeding in the milk in the glass. But these difficulties are entirely got over by adding a minim of the milk to ten minims of boiled water in a purified glass, and using this first dilution both for the estimation of the bacteria and for furnishing the drop to be diluted for the purpose of inoculation. The milk having been well mixed with the water, the bacteria are pretty equally distributed through it, while the addition of so much water to the milk greatly retards the development of the bacteria and makes hurry unnecessary. Thus, I ascertained in one instance that the rate of increase in some milk so diluted and still kept protected in a pure glass appeared to have been only such as to treble the number of bacteria in sixteen hours, whereas they would probably have been multiplied fourfold in two hours if the milk had remained undiluted. The dilution has the further advantage that it does away entirely with the difficulty caused by the milk globules and molecules in the recognition of the bacteria in undiluted milk, even when in very thin layer. In counting the bacteria I found it convenient to take all the fields in succession both in the horizontal and in the vertical diameter of the covering glass, which with my microscope gave about a hundred fields from which to estimate the average.

by all to afford a conclusive demonstration that the particular species of bacterium which we have been studying is really the cause of this special fermentation.[1]

It is true that this proof applies only to one particular kind of fermentative change. But the same method will, I believe, be found applicable in other instances for the purpose of ascertaining how far the rule is universal that a true fermentation, by which I mean one characterized by the faculty of self-multiplication of the ferment, is caused by the development of an organism. In the meantime, as a contribution of a definite character, so far as it goes, to the elucidation of the nature of fermentative changes, so fraught with interest at the present day alike to the physician and the surgeon, I trust it will be not considered unwelcome to the Pathological Society.

There are some other points which came out in the course of this inquiry to which I should like to allude. One of these has reference to the cause of the odour of souring milk. In the lactic fermentation the sugar of milk is resolved into lactic acid by a mere rearrangement of its constituent atoms, one atom of sugar of milk going to form four atoms of lactic acid, without gain or loss. Now the chemist tells us that lactic acid is non-volatile, and accordingly this acid in the pure condition is absolutely odourless. Why, then, should souring milk have any odour ? In fact this investigation has proved, as a result of isolating the true lactic ferment, that the smell of souring milk is principally due to the products of some other concomitant fermentation or fermentations. For when a glass of pure milk is made to sour under the influence of the *Bacterium lactis* pure and unmixed, the odour that results is extremely trifling. Nevertheless the air in the glass shade over a vessel containing milk in such circumstances has a slight sharp odour ; and it seemed worth while to ferment a considerable quantity of milk in this way and subject it to distillation, so as to ascertain, if possible, the nature of the odorous ingredient. Having curdled boiled milk in a purified flask by means of pure *Bacterium lactis*, I mixed six ounces of the recently formed clot with five ounces of distilled water, and having introduced it into a retort, heated it for some hours in a bath of boiling water, the distillate being collected in a receiver kept cool with cloths over which cold water con-

[1] Strictly speaking, the expression should be, not ' the cause ', but ' the cause under ordinary circumstances '. For our facts do not of course exclude the possibility of the existence of some other ferment which might produce the same effect upon milk if the circumstances were favourable to its development, as, for example, by the exclusion of the *Bacterium lactis*. In truth, I once obtained as the result of taking milk directly from the cow into a purified vessel, a minute moving bacterium, which, though it developed very slowly in comparison with the *Bacterium lactis*, produced in time a sour curd, which I have little doubt was due to the change of milk-sugar into lactic acid. But thus interpreted, the terms in the text may be considered admissible ; just as we speak of the yeast plant as the cause of the alcoholic fermentation, although we know that the *Mucor racemosus*, when growing unmixed in a saccharine solution, gives rise to the same fermentative change.

stantly streamed. The product, which by that time amounted to 5½ drachms of clear watery liquid, had the sharp odour of the clot, but in a more concentrated form. It was collected in three successive portions, the last of which had comparatively little of the sharp smell, and rather an odour like that of bread. That which first came off had such a sharply piercing smell that I felt no doubt that it was acid. To my surprise, however, I found it not only tasteless, but neutral to test-paper. I redistilled the product, and stopping the process when half had passed over, found the second distillate still more sharp in odour that the first, while the residue was almost odourless. But on distilling a third time I got a result less pungent than that of the second process, in consequence, I presume, of loss of some of the ingredient through extreme volatility. I kept the last distillate in a stoppered bottle for two days, at the end of which time it still retained its peculiar odour. What the nature of this substance is remains to be determined. It seems likely that it may be some ethereal product with the remarkable peculiarity of having an acid smell, though tasteless and neutral in reaction.

It has been ascertained by Pasteur that the alcoholic fermentation, which, as we all know, consists in the main of the resolution of sugar into alcohol and carbonic acid without gain or loss of atoms, is attended with the appearance of other products in small quantity, such as glycerine and succinic acid, and the ethereal substance in souring milk may, perhaps, be related to the lactic fermentation in a similar manner. I cannot but think it likely that these apparently secondary products may, in reality, be of primary importance in the production of fermentative changes. Pasteur has shown that if yeast is added to a saccharine solution adapted for the nutrition of the *Torula Cerevisiae*, and the liquid is exposed in a thin layer in a shallow vessel to the atmosphere, the torula develops with peculiar rapidity, but little alcoholic fermentation results; and, on the contrary, when the liquid is placed in a deep vessel in considerable mass, the torula develops comparatively slowly but gives rise to abundant fermentation. And he explains this remarkable result by supposing that the fungus requires oxygen for its nutrition, and when it cannot obtain it otherwise, abstracts it from the sugar, and so occasions the fermentation; but when it can get the needful oxygen readily from the air, as it is able to do in the shallow vessel, it thrives peculiarly well, but, not having occasion to withdraw oxygen from the sugar, leaves it undisturbed, except the comparatively small portions of it which it assimilates for its own growth.[1]

[1] Monsieur Pasteur expressed this view in 1861 in a *Bulletin de la Société Chimique*, where, after relating the facts referred to in the text, he thus expresses himself:—'Il paraît dès lors naturel d'admettre que, lorsque la levûre est ferment, agissant à l'abri de l'air, elle prend de l'oxygène au sucre et que c'est là l'origine de son caractère de ferment.' In his recent work, *Études sur la Bière*, 1876, M.

The fact is certainly of extreme interest, because it seems to show that the breaking up of the sugar is not due to the mere presence of the growing organism in its vicinity ; otherwise the fermentation would be proportioned to the growth of the torula, and would therefore be more abundant in the shallow vessel. But the explanation of the difference of the results, as dependent on the necessity or otherwise of abstraction of oxygen from the sugar by the torula, seems to lack applicability without some addition to the hypothesis. For sugar does not lose any oxygen at all in being converted into alcohol and carbonic acid, and therefore the withdrawal of that element would be incompatible with the new arrangement of the atoms in a saccharine molecule.

On the other hand, if we compare the formulae of glycerine and succinic acid with that of sugar, we see that the abstraction of an atom of oxygen from each of several atoms of grape-sugar might naturally lead to the simultaneous formation of the less complex atoms of the other substances out of the residual constituents of the sugar ; the formation of the succinic acid involving the liberation of a certain amount of hydrogen, which again is required for the production of the glycerine : and further, that the relative proportions by weight in which the new compounds would be formed would be those in which they were actually found to present themselves by Pasteur in alcoholic fermentation.[1]

Thus the formation of the glycerine and succinic acid seems to be exactly explained by Pasteur's theory of the deoxidizing agency of the torula upon sugar. But in order to account for the disruption at the same time of a very

Pasteur quotes these first expressions of his theory, and adds that they ' n'ont rien perdu de leur rigueur ; bien au contraire, le temps les a consacrés ' (op. cit., p. 257). When stating his present opinion he employs, it is true, terms which might seem capable of a different interpretation, viz. : ' La fermentation par la levûre s'est présentée à nous comme la conséquence directe d'un travail de nutrition, d'assimilation, de vie en un mot, effectuée sans gaz oxygène libre. La chaleur consommée par ce travail a dû être nécessairement empruntée de la matière fermentescible, c'est-à-dire au corps sucré, qui, à la manière des corps explosifs, dégage de la chaleur par sa décomposition.' The latter of these sentences might seem to have no necessary reference to the question of abstraction of oxygen from sugar by the plant ; but it is immediately succeeded by the following : ' La fermentation par la levûre semble donc liée essentiellement à la propriété que possède cette petite plante cellulaire de respirer, en quelque sorte, avec l'oxygène combiné au sucre.' Here the original theory is plainly restated, and we are led to infer that the decompositions of the sugar referred to in the former sentence as providing the necessary heat for the work of nutrition result from its deoxidation.

[1] According to Miller's *Elements of Chemistry*, the formulae of the three substances are—Glucose (i.e. grape-sugar), $C_6H_{14}O_7$; Glycerine, $C_3H_8O_3$; Succinic acid, $C_4H_6O_4$. Therefore, 5 atoms of glucose, less 5 of oxygen, are equal to 10 atoms of glycerine, less 10 of hydrogen ; and 2 atoms of glucose, less 2 of oxygen, are equal to 3 of succinic acid, plus 10 of hydrogen. Therefore, 7 atoms of glucose, less 7 of oxygen, leave the elements necessary for producing 10 atoms of glycerine and 3 of succinic acid. Now, the atomic weight of glycerine multiplied by 10 is 1860, and the atomic weight of succinic acid multiplied by 3 is 354, so that the weight of glycerine formed would be between five and six times the weight of succinic acid ; and this is just about the proportion of the quantities of the two materials obtained by Pasteur from fermented sugar (see Miller's *Chemistry*, vol. iii, p. 161).

much larger number of other sugary particles into alcohol and carbonic acid, it would seem necessary to assume further that the decomposition of some atoms of glucose into glycerine and succinic acid, under the deoxidizing agency of the torula, exercises a disturbing influence upon neighbouring particles and leads to their becoming broken up into simpler compounds without loss of atoms. Such a theory of the alcoholic fermentation of sugar would be a combination of the views of Pasteur and of Liebig ; and while assigning with the former authority the primary and essential place to the growing organism, would admit with the latter a catalytic influence exerted by decomposing organic substances upon unstable compounds in their vicinity. And if this be the true state of the case, it will be seen that the glycerine and succinic acid, though produced in comparatively small quantity, so far from being secondary and unimportant, are in fact the primary effect of the action of the torula upon the sugar, of which the formation of alcohol and carbonic acid is a secondary, though simultaneous, result. And it is considerations such as these which seem to me to invest with special interest the occurrence of the odoriferous ethereal product above referred to as an accompaniment of the pure lactic fermentation.

This theory of the alcoholic fermentation has the advantage that its principle is applicable not only to cases in which the organisms concerned thrive, like the *Torula Cerevisiae*, in the presence of free oxygen, and may be therefore supposed to be ready to take that element from fermentable materials when they cannot get it in the free condition,[1] but also to fermentations like the butyric, where, as M. Pasteur himself has shown, the long and actively moving bacteria which appear to constitute the ferment, instead of thriving in free oxygen, are rendered incapable of development by it, if not deprived of vitality altogether.[2] There seems no reason for supposing that an organism upon which oxygen in the uncombined condition operates as a poison, should be specially disposed to abstract that element from its combinations. We have in fact, here, the converse of the conditions of the *Torula Cerevisiae*. But nothing is more natural than that such a bacterium, when growing at the expense of an organic material, should take for the purposes of its nutrition some of the atoms composing that substance and leave the rest to form new combinations ; and the decompositions arising in this manner may operate with catalytic effect upon neighbouring

[1] Another well-known instance of this is presented by the common mould, *Mucor racemosus*, which, when growing at the surface of a saccharine solution, produces little or no alcoholic fermentation, but brings about that change in very considerable amount when compelled to grow below the surface where but little free oxygen is at its disposal. M. Pasteur has also demonstrated that even *Penicillium glaucum* and *Aspergillus glaucus* have the same effect, though in a much more limited degree, when placed in similar circumstances. (Vide *Études sur la Bière.*)

[2] To use M. Pasteur's own words, the atmosphere acts upon them with 'influence *mortelle*' ; the italics are the author's (*Études sur la Bière*, p. 293).

particles, whether of the same body or of some other unstable compound present in the solution. For, according to this view, it by no means follows that the substance which is the main subject of a fermentation must be that on which the ferment primarily acts, or indeed, that it should contribute at all to the nutrition of the growing organism. Thus, so far as I am aware, it is, in the present state of our knowledge, an open question whether in the case of the lactic fermentation, as it occurs in milk, the *Bacterium lactis* may not derive its nourishment exclusively from the caseine, the decomposition of which may act catalytically upon the milk-sugar. In that case the old view of the caseine being the ferment would have so much of truth in it that, though not the primary fermenting agent, it would occupy the position of an intermediary between the organism and the material which undergoes fermentation.

In the more typical fermentations, such as the alcoholic and the lactic, the most characteristic and striking phenomenon is the catalysis or breaking up of an organic substance into simpler compounds out of all proportion to what is required for the purposes of the nutrition of the fermentative organism : but it would surely be a great mistake to restrict the term fermentation to cases like these. The only safe ground for us to take is, I believe, to regard as fermentative all chemical changes brought about by growing organisms in the media which they inhabit, whether those changes correspond or not with the immediate necessities of the organism. Thus the mouldy smell produced by the growth of *Penicillium glaucum* in paste or preserve is proof of the formation of some volatile product at the expense of the material in which the fungus is growing. The chemical change thus indicated must, I conceive, be grouped with the true fermentations, whether the penicillium does or does not cause more organic particles to be decomposed than actually contribute to its nutrition. And in like manner I should regard putrefaction as a fermentation without reference to the question whether the amount of albumen decomposed is or is not more than is required for the growth of the putrefactive bacteria. It is nevertheless desirable to give some distinctive appellation to fermentations such as the alcoholic and the lactic, in which the breaking up of the fermentable material occurs out of all proportion to the requirements of the organism concerned ; and for such cases I would venture to suggest the designation *catalytic fermentations*. For certain it is that catalysis, or breaking up of organic substances into simpler compounds, without loss or gain of atoms, does take place in those fermentations, whether in the manner above suggested or otherwise ;[1] so that the proposed term would express an ascertained truth, independently of any theory.

[1] Liebig threw out the suggestion that the yeast plant may by its growth produce a material capable

The lactic fermentation, then, resembles the alcoholic in being a typical catalytic fermentation, the milk-sugar being broken up into lactic acid without loss or gain of atoms, while the simultaneous appearance of another product in small quantity presents another feature of similarity. A further point of apparent analogy between these two fermentations has been brought out by the investigation which forms the subject of this communication. In the experiment of inoculating ten glasses of pure boiled milk with drops calculated each to contain on the average a single *Bacterium lactis* [1] five of the glasses were capped liqueur-glasses such as have been above described, but the other five were in the form of test-tubes with suitable caps, employed in order that I might be able to transport them to London without spilling the milk. The milk was in about the same quantity in the two sets of vessels ; but the test-tubes being narrower than the liqueur-glasses, the contained milk in the former had about twice the depth and a considerably smaller free surface, affording much less opportunity for the access of the atmosphere to the milk. The result was a very marked difference in the times of coagulation of the milk in the two sets of glasses ; that in the test-tubes, where clotting took place at all, being solid within three and a half days of the time of inoculation ; whereas the milk remained fluid in all the liqueur-glasses till about twelve hours later, and in some of those glasses which ultimately curdled the change did not occur till nearly twenty-four hours after it had taken place in the test-tubes. Or in other words, assuming that the curdling of the milk implied the formation of a certain amount of lactic acid, it appeared that the more free exposure to the air in the liqueur-glasses had exercised a retarding influence upon the lactic fermentation in them. The facts, therefore, reminded me of Pasteur's observations as to the effect of atmospheric exposure in checking the alcoholic fermentation. In the time that has passed between the delivery of this communication and its publication I have made an attempt to verify the observation, and also to ascertain whether the analogy with the corresponding fact in the alcoholic fermentation was real or only apparent. For oxygen might be conceived to retard the lactic fermentation in either of two ways : either on the same principle as in the alcoholic fermentation, by supplying an element necessary for the nutrition of the organism, and so preventing the operation of its deoxidizing agency, with attendant catalysis, or on the totally opposite principle of the free oxygen

of acting upon sugar in the same manner as emulsin acts upon amygdalin, one of the most beautiful examples of pure catalysis known to chemists. Pasteur alludes to this suggestion in his work above referred to (*Etudes sur la Bière*, p. 315) as conceding the point for which Pasteur has always contended, viz. that the organism is the primary and essential fermentative agent. And though it seems hardly called for in the case of alcoholic fermentation in presence of Pasteur's facts, yet it seems not at all improbable that the principle may be found to apply to some of the catalytic fermentations.

[1] See p. 373.

operating upon the *Bacterium lactis* as a poison or sedative, as it has been shown to act on the bacterium of the butyric fermentation. The inquiry has assumed larger proportions than I had anticipated: but I may briefly mention here some of the facts ascertained. I found that when I imitated Pasteur's experiment with the fermenting saccharine solution and exposed milk from a dairy in a thin layer to the atmosphere with arrangements for avoiding evaporation, the souring of the milk was retarded to a much greater degree than I had observed it in the comparatively thick layer in the liqueur-glasses of the former experiment. This effect became still more marked when oxygen was substituted for atmospheric air: but the unexpected fact was also elicited that carbonic-acid gas is still more potent than oxygen in retarding the lactic fermentation. The relations which these gases bear to the growth of the *Bacterium lactis* must be reserved for future consideration.

I have introduced into this diagram a representation of the *Torula Cerevisiae* side by side with the *Bacterium lactis*, drawn on the same scale enlarged from camera-lucida sketches (the sketches are reproduced on their original scale in Plate XIV, Figs. 9 to 12). My object in so doing is to bring out the remarkable contrast between them in point of magnitude. This is especially striking if we compare the *Torula Cerevisiae* with the *Bacterium lactis* as it was found after growing for three days in milk diluted with 1200 parts of boiled water (Fig. 11). Here they have assumed a condition so minute that the individuals of every pair do not equal in size the smaller granules of the torula. Being motionless, I could hardly have recognized them as bacteria except from their mode of grouping and the circumstances under which they occurred. Yet *Bacterium lactis* they undoubtedly were, and one such barely visible granule introduced into a gallon of uncontaminated milk would lead within three days to its conversion into a solid mass. It is a ferment just as potent as the torula in spite of its extreme minuteness; and this circumstance, it seems to me, has an interesting bearing upon pathology. For it cannot be said to be an unlikely thing that other organisms may exist as much smaller than the *Bacterium lactis* as that bacterium is than the torula. But if this be the case, such organisms must be entirely beyond the range of human vision aided by the best microscopes that we possess. Seeing, then, that the hypothesis which I make cannot be regarded as extravagant, it will not do for us to say, because we cannot see under the microscope any organisms in a given infective liquid, that they certainly do not exist, and that therefore we must abandon the idea to which analogy might otherwise lead us, that the virus concerned may be of the nature of an organism. We see, I say, from the comparison of these two sketches, that it is far from being impossible that there may exist ultra-microscopic organisms as real, as distinct in structure, and as potent in their effects, as is the *Bacterium lactis*.

But while we have thus reason to think it not unlikely that ultra-microscopic fermentative organisms may exist, we have no grounds whatever for believing that bacteria visible under the microscope have ultra-microscopic germs. The sole reason for the frequently expressed opinion, I may almost say axiomatic assumption, to that effect is, I believe, the fact that while ordinary water has been shown to cause the development of bacteria when introduced into organic liquids even in small quantity, yet no bacteria can be discovered in it by aid of the microscope. But we are apt to forget how extremely difficult it is, with the very high magnifying powers which it is needful to use, to discover such minute objects as bacteria unless they are present in large numbers. Now, if we recall the experiments above related of inoculating milk with very minute drops of water,[1] we see that in the sample of ordinary tap-water examined there could not be more than about one particle capable of producing a bacterium in every 1–100th minim. A drop of that size, small as it is, would, if placed between two flat plates of glass for microscopic examination, spread itself over a space about half a square inch in area, and we might search such a drop for an entire day without finding an individual bacterium contained in it. I once took the trouble to try whether I could find the *Bacterium lactis* in some milk diluted with boiled water to the degree requisite to produce on the average one full-sized individual to every hundredth of a minim, but failed to do so with a protracted search. But the difficulty would have been immeasurably increased if the bacterium had resided for three days in the water and had acquired the characters represented in Plate XIV, Fig. 11, so minute and indefinite that an individual, if placed fairly in the field of the microscope, would probably not attract attention at all, or if it did so, would be passed over as of uncertain nature. In this connexion I may mention a hitherto unpublished observation which I made five years ago. I introduced some tap-water into three capped liqueur-glasses, purified by heat, and placed under glass shades. After a week had elapsed, on taking the glasses into a dark room and examining the water, with a candle placed on the other side of the vessel (a very good way of detecting the first appearances of nebulosity produced in a transparent fluid by bacteric development), I could just discern upon the free surface a delicate bluish film, which, on microscopic examination, proved to be composed of closely packed motionless bacteria of various forms, and for the most part of extreme minuteness. This explained an appearance which had before puzzled me, viz. that when water had been left undisturbed in a wine-glass for a day

[1] See p. 365.

or two, minute bacteria had shown themselves in a drop withdrawn from it, and applied between the immersion lens and the glass that covered the object. Along with the drop I had, no doubt, taken a portion of a bacteric film on the surface. Adult bacteria, therefore, do, as a matter of fact, exist, though it may be in a very minute condition, as a scum on still water, and there can, therefore, be no reasonable doubt that they exist also disseminated through moving water, but detached from one another by the motion of the liquid, so as no longer to present the recognizable characters which they have, even though extremely minute, when packed together in the form of a scum.[1] And supposing them present, thus minute, motionless, and isolated, and as widely scattered as our experiments proved them to be in the water investigated, any attempt to search for them with the microscope would be, I do not hesitate to say, absolutely hopeless.

Our morphological knowledge is also opposed to the idea that bacteria should have germs related in point of magnitude to the adult organism as the seeds of a poppy or the spores of a fern are to the full-grown plant. It is true that there are some species of bacteria in which appearances have been seen that appear to indicate the existence of spores, notably in the case of the *Bacillus anthracis*, which seems to constitute the virus of malignant pustule.[2] But in all such cases the supposed spore or germ is not only conspicuous from its highly

[1] The minute form in which the *Bacterium lactis* was found in milk much diluted with water is only an extreme degree of what was seen under other circumstances. It has been before mentioned (p. 374) that as the souring of milk proceeds the bacteria assume a smaller size. Also when growing in urine, though they presented in the early days the same dimensions as in milk, they were found much smaller at a later period, though still proved by experiment to retain the property of inducing the lactic fermentation in milk. Again, the *Bacterium lactis* which has been described as growing slowly in Pasteur's solution at the expense of a little piece of curd, was almost as small as that in the milk diluted with water. The puny character of the progeny depends probably upon unsuitable or inadequate supply of nutritious material; and in comparison with the media in which bacteria ordinarily thrive, the elements for their nutrition are extremely scanty in water. Again, as regards moving bacteria, it is a very common thing to see them become, not only of smaller size, but motionless as they continue to develop in one and the same medium. A good example of this in a bacterium of unusual form is given in the paper in the *Microscopical Journal* before referred to (p. 17 and Plate XIX; p. 321 and Plate XI of this volume). It is, therefore, not surprising that moving bacteria should, as a rule, acquire motionless as well as minute characters in water. At the same time it is easy to understand that some particular bacteric species, like multitudes of algae and infusoria, may have water as their favourite habitat, and attain in it their largest dimensions.

[2] See especially a memoir recently published in the *Quarterly Microscopical Journal* (vol. xviii, new ser.), by Dr. Ewart, who has observed that the highly refracting bodies which form in the threads that constitute the organism become free and afterwards multiply by segmentation, and that the individuals which result from this fissiparous proliferation again give origin to threads. M. Pasteur describes highly refracting spots, which he believes to be of the nature of germs, in some other bacteria (*Études sur la Bière*, p. 295); and I have myself seen what I have regarded as nuclei in the finely granular protoplasmic mass of some large bacteria, and I have sometimes observed the threads cleared of granular material, as if the nuclei were on the point of becoming free, appearances corresponding so far to those in the *Bacillus anthracis*.

refracting character, but attains dimensions about equal to the transverse diameter of the thread in which it grows.

Nor have we any right to assume that because some kinds of bacteria have germs, the same must necessarily be the case with all. *A priori* there would seem to be no organisms known to us in nature with less necessity for such a provision. They constitute, in fact, in the adult form, a reproductive apparatus; perpetually multiplying with amazing rapidity by fissiparous generation. And further, it seems very likely that bacteria, differing widely as they do in their characters, may spring from various sources. I have, on several occasions, seen appearances which make me think that some bacteria take their origin as segments of the threads of minute filamentous fungi. Certain it is that some such free segments or gemmae, as they are termed by the fungologist, have morphological characters absolutely undistinguishable from some bacteria.[1] And, supposing any bacteria to have such an origin, we may be pretty sure they would not possess germs, seeing that gemmae are themselves a form of germ of the fungi that produce them. In the same way there are ciliated monads which a few years ago would have been unhesitatingly regarded as definite species, but which are now well known to be the spores of various algae and fungi; while there are others which have been proved to be adult organisms with special reproductive arrangements.[2]

The method of investigation which has been described in this communication affords the opportunity of judging regarding any kind of bacterium contained in a particular liquid, whether in reality germs are present as well as the adult form. For if we find that the number of fermentative particles corresponds exactly with the number of adult bacteria which we have counted, we may infer that there were no free germs present in the liquid. Thus we may fairly suppose that the *Bacterium lactis* exists in souring milk only in the bacteric form in which we see it, although it is, of course, possible that it may form germs under other circumstances. Meanwhile the facts which I have adduced will, I hope, remove the mystery attendant on the notion that water teems with ultra-microscopic or invisible germs of the bacteria which we see of larger or smaller dimensions in organic liquids undergoing fermentative changes.

[1] See *Trans. of Royal Soc. of Edinb.*, loc. cit., and *Quarterly Journal of Microscopical Science*, loc. cit.

[2] See the beautiful researches of Dallinger and Drysdale on the life-history of the Monads, *Monthly Microscopical Journal*, August 1, and December 1, 1873; January 1, March 1, and December 1, 1874; and May 1, 1875.

DESCRIPTION OF PLATE XIV

Figs. 1 to 8 represent of natural size certain glasses of unboiled milk described in the text. They are examples of the alterations in appearance produced in milk by various different organisms other than the *Bacterium lactis*. From sketches taken October 1, 1877.

Figs. 9 to 12, camera-lucida sketches, by Mr. Lister, of *Bacterium lactis* and *Torula Cerevisiae* on the same scale, viz. magnified 1125 diameters.

For further description, see the plate and the text.

Plate XIV

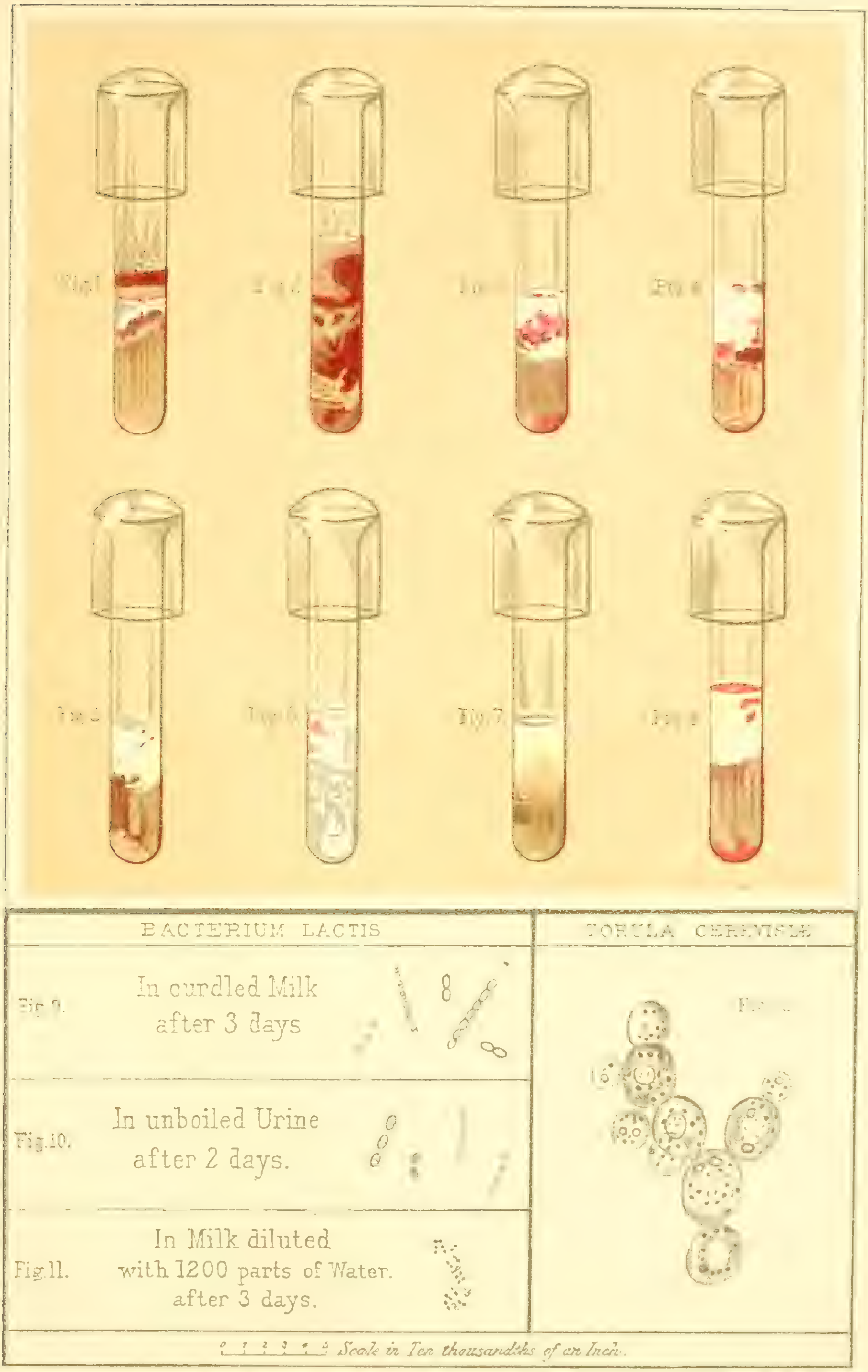


Fig.1
Fig.7
BACTERIUM LACTIS
Fig.9.
In curdled Milk
after 3 days
Fig.10.
In unboiled Urine
after 2 days.
Fig.11.
In Milk diluted
with 1200 parts of Water.
after 3 days.
TORULA CEREVISIÆ
Scale in Ten thousandths of an Inch.

ON THE RELATIONS OF MICRO-ORGANISMS TO DISEASE

An Address delivered before the Pathological Section of the British Medical Association at Cambridge, August 12, 1880.

[*Quarterly Journal of Microscopical Science*, April 1881.]

THE relation of micro-organisms to disease is a subject of vast extent and importance. If we compare the present state of knowledge regarding it with that of twenty years ago, we are astonished at the progress which has been made in the interval. At that time bacteria were little more than scientific curiosities ; whether they were animal or vegetable few people knew or cared, but most regarded them as animals on account of the active movements which they often exhibited. That they were causes of putrefaction, or other fermentative changes, was a thing scarcely thought of ; and the notion that they had special relations to disease would have been regarded as the wildest of speculations.[1] Now, however, a mass of information has been accumulated regarding all these points, of which it would be hopeless for me to attempt to give even a brief sketch in the time at my disposal, and all that I can do is to present to the pathological section a few examples illustrating the progress which is being made in this department of research.

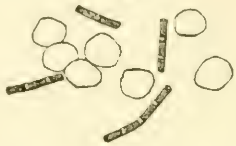
First, I will mention some examples of the labours of Dr. Koch, of Wollstein, in Germany. Though a hard-worked general practitioner, Koch has contrived to devote an immense amount of time and energy to his investigations ; and by a combination of well-planned experiments, ingenious methods of staining bacteria out of proportion to the tissues among which they lie, a beautiful adaptation of optical principles to render the coloured objects discernible by the human eye, and, further, by a most successful application of micro-photography, he has succeeded in demonstrating the presence of these minute organisms in a manner never before attained.

The *Bacillus anthracis* is now universally recognized among pathologists as the cause of splenic fever, so fatal among cattle in this and other countries and capable of being communicated to various other animals, and, among the rest, to the

[1] The bacterium of splenic fever (anthrax) was seen and described by Rayer and Davaine as early as 1850 ; but little was done during the next ten years towards establishing the true relations between the micro-organism and the disease. See *Recherches expérimentales sur la Maladie Charbonneuse*, par H. Toussaint. Paris : Asselin & Cie.

human species, as has been lately illustrated by the so-called 'woolsorters' disease', in the North of England. The *Bacillus anthracis* is a large form of bacterium, as is shown in the accompanying woodcut, *a*. It is there represented magnified 700 diameters, along with the outlines of some red blood-corpuscles of a mouse, and the rods of which it is composed are seen to be in diameter nearly one fourth of that of the red corpuscles. Koch's method of staining sections shows in the most beautiful manner that these bacilli are not only present in the spleen and some other organs, but that they people the blood in the minute vessels of all parts. Koch has thus added to our conviction that the bacillus is the cause of the symptoms, seeing that, as he remarks, it is

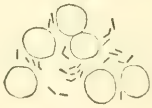
a



impossible to suppose that an organism can develop in such enormous numbers at the expense of the vital fluid without exerting a serious influence upon the system.

But the most striking and important results of Koch's methods of investigation are those which relate to organisms of much smaller dimensions. He found that, if putrid liquid is injected under the skin of a mouse, the animal may die in the course of a short time, as the result of the chemically toxic effects of the products of putrefaction absorbed into the circulation; but, if it survive this primary disorder, it may succumb in the course of about two days to blood disease. If the point of a lancet be dipped into the blood of the heart of a mouse

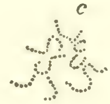
b



which has died in this way, and a scratch be made in the skin of a healthy mouse with the envenomed instrument, the second mouse dies with similar symptoms to those of the first, the poison being absolutely certain in its virulent operation; and the same thing may be continued indefinitely through any series of animals. If now sections of the tissues be made and stained and examined by Koch's procedures, it is found that the entire blood of the diseased animal is peopled with bacteria, resembling those of the *Bacillus anthracis* in the enormous multitudes in which they are produced, and also in their rod-like form, but differing from them in being exquisitely minute and delicate, as is shown in *b* (drawn on the same scale as *a*, as is indicated by the accompanying outlines of red corpuscles), where it is seen that the diameter can only be represented by a slender streak not one-eighth of the diameter of the *Bacillus anthracis*, and such as, before the introduction of Koch's method, would have escaped notice altogether. Now, this disease is totally distinct from pyaemia, being not accompanied with multiple abscesses or embolism ; and thus it has been shown by Koch that septicaemia may exist as a deadly blood disease, caused by the development of micro-organisms, equally distinct from pyaemia and from the chemically toxic effects of septic products.

On some occasions, as the result of the introduction of putrid fluid under the mouse's skin, Koch found, besides septicaemia, a local affection of the seat of inoculation, in the form of spreading gangrene ; and, on investigating the part, he discovered in it, exactly corresponding with the extent of the local affection, another organism very differently formed from that of the septicaemia, viz. a micrococcus, consisting of minute spherical granules arranged in linear series, like strings of exquisitely minute beads, as represented at *c*, which is magnified

c



like *a* and *b* 700 diameters. Believing that this locally developing organism must be the cause of the gangrene, he tried to separate it from the bacillus of the septicaemia, and succeeded through an accidental observation of great interest. Having till that time employed the house mouse in his experiments, he happened to try the inoculation of a field mouse. This animal, though so closely allied, proved not susceptible of the septicaemia. The bacillus of that disease was unable to grow in the blood of the field mouse ; but the micrococcus of the gangrene could develop among its tissues. The new organism was thus obtained in an isolated form, and, when now inoculated into the house mouse, produced in that animal gangrene pure and simple, extending for an indefinite period among its tissues.

Thus the animal body, which had previously been an obscure field of labour in this department, in which the pathologist did little more than grope in the dark, was converted by Koch into a pure cultivating apparatus, in which the growth and effects of the micro-organisms of various infective diseases could be studied with the utmost simplicity and precision.

One more example I must take from Koch's work. On one occasion, as the result of inoculating putrid liquid into a rabbit, he observed a spreading inflammation having all the clinical characters of erysipelas; and, on examining stained sections of the part, he discovered another exquisitely delicate bacillus resembling the micrococcus of the gangrene in being local in its development, while its exact correspondence in extent with that of the disease led fairly to the conclusion that it constituted the *materies morbi*.[1]

I will next refer to a disease occasioned by a micro-organism discovered by the eminent pathologist, Professor Toussaint, of Toulouse, whom I am proud to see present in this Section to-day. This disease has been somewhat inappropriately termed *Choléra des poules*, or fowl-cholera, for it is not attended with diarrhoea or any other of the symptoms of cholera; but, as it happened to be extremely destructive among the poultry-yards of Paris at the same time that an epidemic of cholera was raging in the city, the disorder which prevailed among the fowls was also given the name of cholera. The lesions by which it is chiefly characterized are great swelling of the chains of lymphatic glands in the vicinity of the trachea, pericarditis accompanied with great effusion, and congestion, and it may be ulceration, of the mucous membrane of the duodenum. It is a blood disease, and highly infectious. If some of the blood of a chicken that has died of it be mixed with the oats with which healthy chickens are fed, a considerable proportion, perhaps four out of six, are affected and die; and similar results are produced by mixing the intestinal excreta of diseased fowls with the food. It is an interesting question how the virus thus administered enters the circulation. The invariable affection of the lymphatic glands of the throat suggests to M. Toussaint the idea that some accidental abrasion of the epithelium in the mouth or pharynx is probably the channel; and this view is confirmed by the fact that a similar affection of the lymphatic glands, together with other symptoms of the disease, is produced by inoculating the chicken in the mouth; and further, by the circumstance that such chickens as fail to take the disease when fed with the infected food are liable to it when inoculated, implying that it was merely some accidental circumstance which secured their previous immunity. This disease has been made the subject of special investigation by M. Pasteur. He found that the micro-organism could be readily cultivated outside the body of the fowl. It was, indeed, somewhat particular as regards the fluid in which it would grow; thus yeast-water, in which the *Bacillus anthracis* grows readily, proved an unsuitable medium for this organism, but it grew luxuriantly in chicken broth, and, indeed, in infusion of other kinds of meat; but chicken broth proved peculiarly convenient for the purpose. M. Pasteur has been so kind as to send me some tubes in which

[1] See *Untersuchungen über die Ætiologie der Wundinfectionskrankheiten*, von Dr. Robert Koch Leipzig, 1878. A translation of this work has been issued by the Sydenham Society.

the organism has been cultivated, and a drop of the liquid has been placed under a microscope on the table. It will be seen that the organism is a minute form of bacterium, oval-shaped, tending to multiplication by transverse constriction, and very frequently seen in pairs, and occasionally in chains. Its transverse diameter is from 1–50,000th to 1–25,000th of an inch, so that it resembles very closely the *Bacterium lactis*. The woodcut *d* represents a camera-lucida sketch of the organism sent by M. Pasteur. It is drawn on the same scale as the other illustrations of this paper. So far as I am aware, this is the first time this bacterium has been shown in this country. Now, it was found by Pasteur that the organism could be produced in chicken broth in any number of successive cultivations, and to the last retained its full virulence, so that, if a healthy chicken was inoculated with it, the fatal disease was produced as surely as by inoculation with the blood of a fowl that had died of the complaint. This was pretty conclusive evidence that the organism was the cause of the disease, and that it constituted the true infective element ; because any other material that

d

might be supposed to accompany it in the blood of the diseased animal must have been got rid of by the successive cultivations in chicken broth.

The growth of the organism occasions no putrefaction in the liquid ; so that this is a good example of a bacterium which is most destructive as a disease, but which is at the same time entirely destitute of septic property, in the primitive sense of that term as equivalent to putrefactive. After the bacterium has grown for a certain time in a given portion of chicken broth, it ceases to develop further ; and when this is the case, although the broth has lost only a very small proportion of its substance by weight, and although, as aforesaid, it has not undergone putrefaction, and still constitutes an excellent pabulum for ordinary forms of bacteria, the bacterium of the fowl-cholera, though introduced from some new source, is incapable of growing in it. This fact seems highly suggestive of an analogy with the effects of vaccination, or those of an attack of measles or scarlatina, in securing immunity from the disease for the future. Here we have a certain medium invaded by a virus capable of self-multiplication, as is the case with those diseases in the animal body ; the medium itself little affected chemically by the growth of the virus within it, but nevertheless rendered unfit for the development of that virus for the future. But something more than the suggestion of analogy with vaccination has been effected by M. Pasteur. By cultivating this bacterium in a particular manner, which he has not yet published,[1] he enfeebles the organism, as he believes, and produces such an alteration in it that, when inoculated into a healthy fowl, it produces only a modified, and no longer fatal form of the complaint ; but the bird is thereby rendered secure against taking the ordinary form of the disease. It has been really vaccinated, if we adopt M. Pasteur's extension of the term vaccination to other similar cases ; for just as we speak of an iron milestone, we may, if we please, apply the term vaccination to the use of a virus other than the vaccine obtained from a heifer. But though the vaccination with the modified bacteria of the fowl-cholera does not occasion the fatal disease, it produces pretty severe local effects. If inoculated on the breast of the fowl, it causes a limited gangrene of the pectoral muscle, the affected part falling off in due time as a dry slough. Through the great kindness of M. Pasteur, I have now the opportunity of showing to the Section a hen which has been treated in this way. You observe a slough on the breast of the bird about as large as a penny piece ; it is dry, and obviously old. The fowl has been some days in my possession subsequently to its journey from Paris ; but though more than enough time has elapsed since the inoculation to have caused its death, had the disease been in the ordinary form, it is, you see, in good health, bright and active, and it both eats and sleeps well.[2]

I will now return to the *Bacillus anthracis*, with regard to which I shall have again to refer to the labours of M. Toussaint. First, however, I must allude to the work of some of my own countrymen. In March 1878, an experiment was made at the Brown Institution, at the suggestion of Dr. Burdon Sanderson, of inoculating a calf with the blood of a guinea-pig which had died of splenic fever, which is exceedingly fatal to rodentia. The result was that the calf took the disease, but in a mild form, and recovered from it ; and a similar fact was observed in two heifers treated in the same way.[3]

This line of inquiry has since been followed up by Dr. Sanderson's successor at the Brown Institution, Dr. Greenfield, with a view of ascertaining whether the milder form of the disease in cattle, resulting from inoculation with the blood of rodentia affected with it, confers upon the cattle immunity from the complaint in its fatal form ; or, to use again M. Pasteur's expression, whether the cattle have been vaccinated with reference to anthrax. And I have great pleasure in being able to inform the Section, by Dr. Greenfield's permission,

[1] For an account of M. Pasteur's method of procedure see the notes at the end of this address.

[2] M. Pasteur's researches on this subject are related in the *Comptes Rendus de l'Académie des Sciences*, February, April, and May, 1880.

[3] See 'Report on Experiments on Anthrax', by Dr. Sanderson (*Journal of the Royal Agricultural Society of England*, vol. xvi, s.s., part i).

that the question has been answered in the affirmative; and that one bovine animal, inoculated seven months ago with virus from a rodent, has proved itself, on repeated inoculations, entirely incapable of contracting splenic fever, remaining free from either constitutional or local manifestations of it.

And now to return to M. Toussaint, who has made observations with regard to this same subject of vaccination against anthrax fraught with the very deepest interest. The question arises with regard to effective vaccination, using the term in Pasteur's general sense: Is it essential that micro-organisms should develop in the blood of the animal in which immunity from further attacks of the disease is to be secured? Or is it possible that the necessary influence upon the system may be exerted by merely chemical products of the growth of that organism in some other medium? With the view of approaching the solution of this question, M. Toussaint has performed experiments of injecting into the blood of healthy sheep blood taken from an animal affected with splenic fever, but deprived of the *Bacillus anthracis*. Taking blood from a sheep just on the point of death, when the bacillus has presumably produced all its possible effect upon the vital fluid, M. Toussaint proceeds to deprive it of the living bacillus in either of two ways—by filtration, or by destroying the vitality of the organism. The former he effects by mixing the blood with three or four parts of water, and then passing it through about twelve layers of ordinary filter-paper. The bacillus, in consequence of its large dimensions, is entirely retained by this form of filter, as is proved by the fact that the filtrate no longer gives rise to the organism in a cultivating liquid or in a living animal. Nevertheless, if injected in considerable quantity into the circulation of a healthy sheep, it produces a true vaccinating influence, that is to say, secures immunity from splenic fever. But, what is further extremely interesting, in order that this change in the constitution of the sheep may be brought about, the lapse of a certain time is essential. If a vaccinated sheep be inoculated with anthrax within a few days of the operation, it will die of splenic fever; but if from twelve to fifteen days be allowed to elapse, complete immunity is found to have been produced. Similar results followed from the injection of anthrax blood treated by M. Toussaint's other method, which consists of maintaining it for a considerable time at a temperature of 55° C. (131° Fahr.), which has the effect of killing the bacillus; after which one-half per cent. of carbolic acid is added, to prevent putrefaction of the liquid. The blood treated in this way having been proved to be free from living bacilli by negative results of an experiment upon a rodent, about four cubic centimetres are injected into the venous system of a sheep, with the effect of producing the same protective influence against splenic fever as is ensured by the filtered blood. These experiments are still in progress; but M. Toussaint informs me that he has already ascertained the existence of immunity against anthrax for three months and a half in both the sheep and the dog treated in this way.

I need hardly remark on the surpassing importance of researches such as these. No one can say but that, if the British Medical Association should meet at Cambridge again ten years hence, some one may be able to record the discovery of the appropriate vaccine for measles, scarlet fever, and other acute specific diseases of the human subject. But even should nothing more be effected than what seems to be already on the point of attainment—the means of securing poultry from death by fowl-cholera, and cattle from the terribly destructive splenic fever—it must be admitted that we have here an instance of a most valuable result from the much-reviled vivisection.

I have yet one more example to give of researches in this domain of pathology; and this also has reference to the *Bacillus anthracis*. The investigator in this instance is Dr. Buchner, assistant physician in Munich. It is well known that the *Bacillus anthracis* is morphologically identical with an organism frequently met with in infusion of hay, which may be termed hay-bacillus. Such being the case, it occurred to Dr. Buchner that they might be merely one and the same organism modified by circumstances. For my own part, I am quite prepared to hear of such modifying influence being exerted upon bacteria, having made the observation several years ago that, when the *Bacterium lactis* had been cultivated for some time in unboiled urine, it proved but a feeble lactic ferment when introduced again into milk. Its power of producing the lactic fermentation had been impaired by residence in the new medium. In the case before us, indeed, the physiological difference between the two organisms seems, at first sight, so great as to forbid the idea of anything other than a specific difference. The *Bacillus anthracis* refuses to grow in hay-infusion, in which the hay-bacillus thrives with the utmost luxuriance; and conversely, the hay-bacillus is utterly incapable of growing in the blood of a living animal, whether introduced in small or in large quantities. The hay-bacillus is remarkable for its power of resistance to high temperatures, which is not the case with the *Bacillus anthracis*. The latter is destroyed by a very slight acidity of the liquid of cultivation, or by any considerable degree of alkalinity, whereas the former survives under such conditions. Both will grow in diluted extract of meat, but their mode of growth differs greatly. The hay-bacillus multiplies rapidly, and forms a dry and wrinkled skin upon the surface, while the *Bacillus anthracis* produces a delicate cloud at the bottom of the vessel, increasing slowly. Nothing daunted by these apparently essential differences, Dr. Buchner has laboured with indomitable perseverance, by means of experiments carried on in Professor Nägeli's laboratory, to solve the double problem of changing the *Bacillus anthracis* into hay-bacillus, and the converse. Having devised an ingenious apparatus by which a large reservoir of pure cultivating liquid was placed in communication with a cultivating vessel, so that any cultivation could be drawn off by simply turning a stop-cock, and further cultivating liquid supplied to the organisms remaining in the vessel by a mere inclination of the apparatus, Buchner proceeded to cultivate the isolated *Bacillus anthracis* in extract of meat for several hundred successive generations. As an early result of these experiments, he found that the bacillus lost its power of producing disease in an animal inoculated with it. Up to this point he is confirmed by Dr. Greenfield, who has found that, when the *Bacillus anthracis* is cultivated in aqeous humour, after about six generations it loses its infective property. Then as Buchner's experiments proceeded, the appearance of the growing organism was found to undergo gradual modification. Instead of a cloud at the bottom of the vessel, a scum began to make its appearance—at first greasy-looking and easily broken up—constituting, so far as appearances went, an intermediate form between the two organisms ; and in course of time the scum became drier and firmer, and at length the modified *Bacillus anthracis* was found to be capable of growing in an acid hay-infusion, and to present in every respect the characters of the hay-bacillus. The converse feat of changing the hay-bacillus into the *Bacillus anthracis* proved very much more difficult. A great number of ingenious devices were adopted by Buchner, who was, nevertheless, continually baffled, till at last he attained success in the following manner : Having obtained the blood of a healthy animal under antiseptic precautions, and defibrinated it also antiseptically, and having arranged his apparatus so that the pure defibrinated blood, which was to be the cultivating medium, should be kept in constant movement, continually breaking up the scum, and also keeping the red corpuscles in perpetual motion so as to convey oxygen to all parts of the liquid—in this way imitating, to a certain extent, the conditions of growth of the *Bacillus anthracis* outside the animal body, within which the hay-bacillus could not be got by any means to develop—he proceeded to cultivate through numerous successive generations. A transitional form soon made its appearance ; but the change advanced only to a limited degree, so that further progress by this method became hopeless. The modified form hitherto obtained failed entirely to grow when injected into the blood of an animal. On the contrary, it was in a short time completely eliminated from the system, just like the ordinary hay-bacillus. It had, however, been observed by Buchner that spores had never been formed by the bacillus growing in the defibrinated blood ; and it occurred to him that, perhaps, if it were transferred to extract of meat, and induced to form spores there, the modified organism might yet grow in the blood of a living animal. The carrying out of this idea was crowned with success; and, by injecting various different quantities of the liquid containing the organism into different individuals, Buchner at length succeeded, both in the mouse and in the rabbit, in developing true *Bacillus anthracis* out of the progeny of the hay-bacillus. When large quantities were introduced, the animals died rapidly from the merely chemical toxic effects of the injected liquid; but in some instances in which a smaller amount was injected, after the period for these primary effects had passed, a fatal disease supervened—attended, as in anthrax, with great swelling of the spleen, the blood of which was found peopled, as in that affection, with newly formed bacilli; and the spleens affected in this way were found to communicate anthrax to healthy animals, just like those of animals which have died of ordinary splenic fever.[1]

Supposing these results to be trustworthy (and the record of them bears the stamp of authenticity), I need scarcely point out to a meeting like the present their transcendent importance as bearing upon the origin of infective diseases, and their modifications as exhibited in epidemics.

I trust that these examples may suffice to convey some idea of the work now going on with reference to the relations of micro-organisms to disease.

Since the above address was delivered, M. Pasteur has published the method by which he produces the 'attenuation' of the virus, or, in other words, the enfeeblement of the organism of fowl-cholera which fits it for securing immunity from the fatal form of the disease. This method consists in cultivating the organism, pure and unmixed, in chicken broth, to which access of air is permitted while dust is excluded, and simply allowing some months to elapse before it is employed. If the period does not amount to more than about two months, the organism retains its virulence little abated, but if the period is extended to three or four months it is found that animals inoculated with the organism take the disease, but have it in a milder form, and a considerable proportion recover; and if the time is made still greater, as, for example, eight months, the organism has so far lost its potency that though chickens inoculated with it still go through an attack of the disease, all recover. If the period is sufficiently prolonged, there comes a time when the organism is found to have lost its vitality altogether, so that it will no longer give rise to new development when introduced into fresh cultivating liquid.

In considering by what agency this enfeeblement of the organism and ultimate extinction of its vitality was brought about under the circumstances

[1] See *Ueber die experimentelle Erzeugung des Milzbrandcontagiums aus den Heupilzen*, von Hans Buchner, München, 1880.

referred to, it occurred to M. Pasteur that it might perhaps be the oxygen of the air admitted to the vessels. Oxygen is essential to the growth of the organism, but it might, as M. Pasteur thought, be, nevertheless, in long-continued action upon it, a cause of weakness. With a view of testing this idea he instituted cultivations of the bacterium in broth contained in tubes partially filled with the liquid, that is to say, containing a certain proportion of their volume of air, but sealed hermetically. The result was a growth of the organism, indicated by turbidity of the clear fluid, attaining a degree proportioned to the amount of air present in the tube, but coming to an end when that air was exhausted, so that the little organism, no longer growing throughout the liquid, fell to the bottom of the vessel, leaving the fluid again clear. The organism having now exhausted all the free oxygen, was from this time forth presumably protected from the influence of that element, and, in exact accordance with M. Pasteur's theory, it was found that no matter how long these closed tubes were kept, the organism retained not only its vitality, but its full virulence, as tested by inoculation of healthy chickens.[1]

There can be no question as to the great importance of these facts; and the medical world must for ever remain deeply indebted to M. Pasteur for eliciting them. Doubts may, however, be entertained regarding the interpretation of the phenomena. Thus Dr. Greenfield, whose own researches have had special reference to the modifying influence exerted upon bacteria by the medium in which they grow, has thrown out the suggestion that the enfeeblement of the organism of fowl-cholera growing with free access of air may be due to alterations in the fluid which they inhabit rather than to the effect of oxygen upon them. When free access of oxygen is permitted, the organism, he contends, will continue to grow till all the material suitable for its nutrition is exhausted, and as the nutriment becomes defective the progeny will be feeble. At the same time this exhaustive development of the organism will be attended by the full measure of possible alteration in the quality of the liquid which the growth of the organism can effect, and this alteration will naturally involve the production of substances which may exert a prejudicial influence upon the organism itself. On the other hand, the bacterium, when growing in a sealed tube with limited supply of oxygen, has its development brought to a stand by the exhaustion of that gas, while the organism is in full vigour and in a fluid but slightly changed from its original wholesome condition. It thus remains like a vigorous seed, ready to start into energetic growth when the conditions for its germination are supplied.[2] The essential difference between the two

[1] See *Comptes Rendus*, October 26, 1880.

[2] See 'The Brown Lectures', by W. S. Greenfield, M.D., &c.; Lecture II, *Lancet*, January 1, 1881.

views may be stated shortly thus: M. Pasteur regards oxygen as a slow poison of the bacterium; Dr. Greenfield seeks for the slow poison in the products of the fermentative agency of the organism.

The time which has passed since the delivery of this address has brought out facts which have led M. Toussaint to take a different view of the nature of the liquid used in his 'vaccinations' against anthrax above referred to. In a letter which he has had the kindness to write to me on the subject, he informs me that on two different occasions injections of anthrax blood treated by one of his methods has led to the death of the animal from anthrax; and in one instance, a similar injection induced a local affection which appeared to have the characters of malignant pustule. He has hence been led to the conclusion that the diseased blood treated by his methods, instead of being (as he at first believed) free from the living bacillus, contained the organism in an 'attenuated' form.

Thus it would appear that the observations of Pasteur, Toussaint, and Greenfield agree in ascribing the 'vaccinating' influence to a modified form of the micro-organism concerned.

Nevertheless some other observations have been made which tend to justify the original line of inquiry pursued by Toussaint. Chauveau has found that if ewes inoculated with anthrax in the last months of gestation recover from the disease, not only are the mothers no longer susceptible, but the lambs enjoy similar immunity.[1] Further, it has been ascertained by others, including Dr. Greenfield, that the blood and tissues of the foetus of an animal dying of anthrax contain no bacilli, while those of the mother swarm with them. Putting these two observations together we are led to the inference that while the integrity of the placental vessels prevents the bacilli from entering the foetal circulation, the foetus is so dosed with soluble products of the development of the bacilli in the maternal blood as to be rendered proof against the disease.

[1] See Dr. Greenfield's First 'Brown Lecture', *Lancet*, December 18, 1880.

AN ADDRESS ON THE RELATIONS OF MINUTE ORGANISMS TO INFLAMMATION

Delivered in the Pathological Section of the International Medical Congress, August 5, 1881.

[*Transactions of the International Medical Congress*, London, 1881.]

Mr. President and Gentlemen.—In opening a discussion on the subject of the relations of micro-organisms to disease in general at the meeting of the British Medical Association at Cambridge last year,[1] I brought forward what seemed to be some established facts illustrating the connexion between minute organisms and certain specific disorders, both constitutional and local. I dwelt especially upon the admirable investigations of M. Pasteur into the *Choléra des poules*, and those of Toussaint and others into malignant pustule or anthrax, and the exceedingly beautiful results obtained by the experiments and methods of Dr. Koch. This morning we have to discuss a more limited portion of this great subject—namely, the relations of micro-organisms to unhealthy processes arising in wounds. I have the great satisfaction, gentlemen, of knowing that Dr. Koch is present among us, and also that, with infinite kindness, and very great trouble to himself, he is about to exhibit at King's College, to a limited number, his methods of procedure in actual operation. It is but to a limited number that these demonstrations can be made, because only a very few at a time can see them to advantage ; but I have also the great satisfaction of knowing that Dr. Koch will exhibit this afternoon in this room, by the magic lantern, photographs of sections made by himself of various diseased tissues, illustrating the effects of micro-organisms. These photographs will be as convincing and as satisfactory as the actual demonstration of Dr. Koch's processes, because the pictures drawn by light are entirely free from those errors which can hardly fail to creep in as a consequence of mental bias when a sketch of these minute objects is made by the human hand. Permit me to return to Dr. Koch the thanks of this Section for his great kindness in this matter. Thus the Congress will have an opportunity of seeing confirmed, and indeed extended, the kind of evidence which I brought before the British Medical Association last year.

But while I am more than ever convinced of the importance of the relations of micro-organisms to diseased processes in wounds, I propose this morning to utter what seems to me a needed note of warning against a tendency to exaggeration in this direction. This exaggeration, if such there be, is largely due to the

[1] See p. 387.

success of antiseptic treatment. If we treat our wounds by means expressly calculated to exclude altogether the entrance into them from first to last of minute organisms, not only are the specific diseases got rid of, not only do hospital gangrene and pyaemia, those scourges of former surgery, fly away as at the touch of the enchanter's wand, to trouble us no more for ever, while septicaemia also vanishes, and erysipelas, though more stubborn, is robbed of its terrors—not only, I say, do these diseases, recognized as specific, disappear, but, if the treatment is properly conducted, we get rid of inflammation altogether; and we see wounds that are left with their edges widely gaping, and become occupied by a substantial blood-clot, heal, it may be, without a particle of pus, a cicatrix forming beneath the superficial layers of the coagulum. Such results, proceeding from a mode of treatment designed especially to exclude bacteria, may suggest the idea that all inflammation is caused by micro-organisms, and that suppuration, whether acute or chronic, is always due to similar agencies. Gentlemen, this I believe to be a very exaggerated view of the matter, and a view which may tend to have a serious influence upon our practice. For example, if we believe that inflammations are due only to an invasion of microscopic parasites—if that is the sole cause of inflammation in every case, to what purpose is it to employ counter-irritation? Counter-irritation would seem an absurdity under such circumstances; and accordingly I lately read in a work by a most able surgeon the statement that counter-irritation may be regarded as a thing of the past, as something exploded. Again, in the case of those important diseases which we term strumous, the languid degeneration of tissue which we see in feeble constitutions, there is at the present time a tendency to look upon this as altogether of an infective nature. This also I believe to be an exaggerated view, and one which may injuriously affect our practice. If, for example, I really believe that the degenerated tissue is infected with an invading parasite which is the essence of the disorder, the natural inference will be, that if I am to resect a joint affected with strumous disease I ought to cut out the whole of the diseased structures; I should not be satisfied without cutting away all the degenerated textures, a practice which I believe would often be exceedingly disadvantageous to our patients.

Let me say a few words in the first place with regard to acute inflammation. Acute inflammation is certainly very often caused by the products of decomposition, the results of fermentation induced by the development of minute organisms. Of that we have abundant proof; but we have also sufficient evidence, as it appears to me, that inflammation is often caused otherwise—viz. through the nervous system; that, in fact, the ancient principles of John Hunter with regard to sympathy were true principles. Let us take, for example, the case of irritation of the urethra leading to disturbance of the kidney without any affection of the intermediate parts: the irritation applied to the urethra, the effect produced upon the kidney. This I conceive can only be explained through the nervous system. For instance, I have seen a strong and apparently healthy patient on whom lithotomy had been performed go on perfectly well until the first occasion of the passing of urine through the urethra as the wound healed. He then had a violent rigor, and from that moment there was complete suppression of urine. Death occurred from uraemic poisoning, and upon post mortem examination I found what had apparently been previously perfectly healthy kidneys affected throughout with most intense inflammatory congestion. That I can only explain as occurring through the nervous system, by virtue of nervous sympathy existing specially between one part of the urinary tract and another. Again, I have known a medical man affected with stricture pass, after an interval of many years, a bougie upon himself. The first time he passed water after this had taken place he felt a cutting sensation in the urethra, and had a violent fit of shivering. He had all the appearance of being likely to follow the same course as the other patient—viz. that death would result from uraemia. He sent for me when suppression of urine had already fully declared itself. I had a piece of thin macintosh cloth put under his back, and on this piece of macintosh cloth, between it and the loins, I had placed a large mass of flannel wrung out of boiling water as hot as it could be applied, and the macintosh cloth drawn rapidly round the body and fixed in position with a sheet pinned over it. He, a medical man, accustomed to observe, told me afterwards that the effect of this seemed to be like the operation of a charm. He experienced an immediate sense of relief, and in a very short time he passed water again, the kidneys resuming their functions. Inflammatory congestion, caused sympathetically by irritation in the urethra, had been got rid of, and that by virtue of something acting on the principle of counter-irritation—an irritant applied to the skin of the loins, the part of the surface which is most in sympathy with the kidneys. It is the same sort of sympathy by virtue of which the accoucheur can induce the contraction of a relaxed uterus by applying a cold wet towel to the hypogastrium and the vulva—the special sympathy which, as John Hunter pointed out, exists between an internal organ and the integument nearest to that organ.

Then, to take a very simple case, let me refer to the result of tight stitches. I once saw in a patient, about three days after removal of the mamma, where the edges of the wound had been brought together by interrupted sutures unusually tightly applied, an inflammatory blush extending up to the collar-bone. I took out the stitches and watched the result; the fiery redness faded away before my eyes, and in a few minutes was almost entirely gone. That redness was indubitably brought about by sympathy ; the stitches acted upon certain nerves, and through the nervous system the inflammatory disorder was produced. I imagine that all physiologists will admit that determination of blood might be induced through the nervous system. But it is not only this effect that we see from tight stitches ; we see also in time oedema, and we may even see death of tissue from the violence of inflammatory disturbance in the more immediate vicinity of the stitch, though the stitch only acts directly upon a microscopically small portion of the tissue.

Counter-irritation seems to be based upon a law in physiology, which I may take the liberty of illustrating by some simple examples. Suppose a fly settles upon the skin of the face : we experience an intolerable sense of itching ; we rub the part with the finger, and the itching disappears—a fact familiar to all the world. But now I find that the same effect of removing the sense of itching takes place if, instead of rubbing the actual spot on which the fly settled, I rub in a ring round it, without touching the spot at all. What is the interpretation of those facts ? In the first place, I suppose the sense of itching depends upon an abnormal action of the sensory nerves of that particular spot on which the fly settled. By rubbing a ring in the vicinity I call into play a strong action of the sensory nerves of a neighbouring part of the skin which is in sympathy with that part on which the fly settled, by virtue of the same nervous connexion through which the skin of the chest blushed as the result of a tight stitch. And this new nervous action occurring leads to the cessation of the abnormal action which was previously going on ; as if the attention, so to speak, of the nervous system were distracted from the affected part. That may seem a very homely illustration ; but if the interpretation is correct, it serves the purpose none the worse on that account. Suppose, again, we feel a sense of irritation in the Schneiderian membrane—a sense of irritation which, if it goes on, will relieve itself by the violent action of the expiratory muscles which we term sneezing ; and supposing we are desirous that this act should not take place—it would be inconvenient, perhaps, that we should sneeze—if with the hand we violently rub the tip of the nose so as to produce a considerable sense of uneasiness there, the sneeze is prevented. I do not touch the part affected with the abnormal sensation, but I call into play a strong action of the nerves in a part which is in sympathy with it—a part of the same nasal organ—and by so doing I cause the previous action to cease. That is another simple but instructive example of physiological counter-irritation.

Take one more instance. I was once asked to see a young woman, previously in perfect health, who, taking her broth—‘ kail ’, as the Scotch call it—

very voraciously, swallowed the bud of the kail plant, and this became impacted in the upper part of the oesophagus. Of course she could not swallow, and she came to my house surgeon to be relieved. He made certain attempts, which were not successful, and three days after the accident I was asked to see her. During these three days she had remained in apparently perfect general health; she had her usual florid complexion, the pulse was absolutely undisturbed; the tongue, too, it so happened, was perfectly clean. But, what was very remarkable, she had had no sense of hunger for those three days; but she had had a curious yearning sort of uneasiness in the epigastrium, induced by the presence of the foreign body in the oesophagus, and this abnormal sensation, caused by the object in the oesophagus, had taken the place of hunger. By virtue of the sympathy existing between the oesophagus and the stomach, the sensation, or nervous action, which constitutes hunger had been prevented from occurring. I extracted the bud which was plugging her oesophagus, and the normal sensation of hunger soon returned. Here, then, was another example of physiological counter-irritation—a term which I have ventured to apply to cases in which the excited nervous action which the counter-irritation removes has not overstepped the limits (indefinite though they be) which separate health from disease.

It appears, then, that it is a law of physiology that when two parts are nervously in sympathy with each other, if we excite a great action in the nerves of one we may distract action from the nerves of the other. Now this will serve to throw great light upon the nature of inflammation itself if we find that counter-irritation is really a valuable means for the treatment of inflammation. That such it is I will only give one or two illustrations. I once fell upon the ice with my knee bent, striking the knee and producing at once a severe strain and a severe contusion. The knee became violently inflamed, the inflammation being characterized by intense pain and effusion into the knee-joint. I treated myself by a splint to ensure rest, and hot fomentations. Every time a fresh hot fomentation was applied, though the heat was so great as to be painful to the skin of the knee, I rejoiced in it on account of the removal of the pain from the interior which always attended it. I remember once having a severe attack of sore-throat, and a mustard poultice was put on of pure mustard and water. The mustard, of course, caused a burning sense of uneasiness in the skin of the throat; but it was a delightful sensation to me, because I felt that while this burning uneasiness was caused to the skin, the sharp cutting pain of the interior of the throat was at once attacked, and gradually disappeared under the influence of the counter-irritant. Experiences like these in one's own person have a more convincing effect than reports from the lips of patients.

Let me give one more example, and that is the effect of the actual cautery in certain forms of articular disease. When I went first to Edinburgh, the thing that struck me most was the effect of the cautery as applied by Mr. Syme in certain cases of joint disease. The first instance of this which I saw was a young woman with an exceedingly painful affection of the shoulder-joint. It was not hysteria, for there was atrophy of the deltoid muscle from instinctive disuse, and the disease was marked by intense pain, extending to the finger-tips, instead of being limited to the joint, as it would be in hysteria. The pain was, at the same time, worse at night, depriving her almost entirely of sleep, and it was accompanied by other abnormal sensations. Mr. Syme applied the actual cautery of red-hot iron before and behind the joint, and when the patient woke up from the chloroform sleep the pain was gone, and never returned; and the disease, which had been going on and gradually progressing for months, was cut short from that time, and before long she left the hospital with a well-developed deltoid muscle. Several cases of a similar nature happened to occur about that time. One was that of a young man with 'ulceration of cartilage' in the articulations between the occiput and the atlas, and between the atlas and the axis. The disease caused exquisite agony, shooting down to the shoulders and up into the head. The patient could not raise his head from the pillow without supporting it with his hand; he could not look up to the ceiling or turn his head at all to one side without moving his whole body Here, again, the pain was worse at night, and that the disease had already produced great effects was evident from the fact that on examining the throat with the finger we felt an irregular prominence of the bodies of the vertebrae in the posterior wall of the pharynx. Mr. Syme applied the cautery to the skin of the back of the neck over the upper cervical vertebrae, and though in this instance the abolition of pain was not immediate, but took place more gradually, this most formidable inflammatory disorder, which had long resisted other forms of treatment, went on steadily to complete cure; and that the cure was permanent was proved by his coming to the hospital some time after to introduce his bride to us.[1]

Now if it be true that counter-irritation is a powerful means of treating inflammation, and if the explanation which I have given of the mode of the action of counter-irritation, as illustrated by the physiological cases, is correct, then I say the effect of counter-irritation in the treatment of inflammation throws great light upon the nature of inflammation itself, and upon the relation of the nervous system to it. If counter-irritation cures an inflammation by withdrawing nervous action from the affected part, it follows that the inflammation so cured was maintained by an abnormal action of the nerves of the part.

[1] See also vol. ii, p. 373.

This conclusion is confirmed by the fact that it is in harmony with and elucidates the mode of operation of the most frequent cause of inflammatory attacks—exposure to cold. How does a chill of the surface lead to an internal organ becoming inflamed ? Why should a draught of cold air upon the chest lead to an attack of inflammation of the lungs ? First, it seems clear that in some way or other the effect is brought about through the nervous system ; for the integument only is chilled, and the deeply seated internal organ suffers, while the same law of sympathy or nervous connexion which we have seen in counter-irritation applies equally here ; it is the cooling of the skin nearest the internal organ that is most likely to cause its inflammation. And further, the cold sometimes 'strikes in' with a suddenness that conveys the idea of a nervous shock, and seems to preclude the hypothesis of any other agency than that of the nervous system. Next we have to ask what immediate effect does cold produce upon the nerves of the surface on which it acts ? One effect which cold certainly does produce is to lower the activity of the nerves on which it operates. In this respect it is the converse of heat. It therefore seems natural to suppose that cold acts in causing inflammation exactly on the converse principle that heat may act in curing it ; a diminution of the action of the nerves of a part of the surface leading to an increased action of the nerves of an internal organ in sympathy with that part. And this view of the matter is confirmed by familiar experience. Suppose a man is liable to inflammatory disorder of the bowels, what is the time when he must be most careful to keep his coat buttoned up when he walks out into the cold air ? It is immediately after taking a hearty dinner ; it is just at the time when there is the greatest amount of physiological activity of the organs liable to inflammation. When the nerves of the internal organ are already doing their utmost consistently with health, then it is that it is most likely to suffer from additional nervous action thrown upon it in consequence of depression of nervous activity in the chilled integument with which it sympathizes—exactly the contrary effect, as it appears to me, to that of the actual cautery, the mustard poultice, or the hot fomentation.

Let me now give a single example of the influence of the nervous system in producing or maintaining chronic inflammation. Suppose a patient comes to us with chronic inflammation of the synovial bursa situated over the patella and its ligament—chronic housemaid's knee. This, as we all know, is a very obstinate complaint, and may have resisted perfect rest, blistering, and a variety of other treatment. If it has existed any length of time, we find that there is not only effusion of fluid into the synovial sac, but inflammatory thickening of the surrounding tissues. Now, I find that if we make a puncture in the sac through the skin with a tenotome and introduce a little drainage-tube not bigger in calibre than a crowquill, at the same time doing this in such a way as to prevent the entrance of putrefaction and employing an efficient antiseptic dressing, we may reckon on it as a matter of certainty that the disease which has been previously so obstinate rapidly becomes cured. We change the dressing in the course of a day or two in order to shorten the tube, and at the next dressing we probably find the serous oozing has been so slight as to permit us to dispense with the tube altogether, and within a week or ten days the little puncture is healed. Meanwhile, not only is there no reaccumulation of fluid, but the thickening of the surrounding tissues disappears rapidly, and before long vanishes altogether. Let us look at the interpretation of this fact. And first let me remark that the treatment which so rapidly causes subsidence of the obstinate inflammatory disorder does not act directly upon the diseased synovial membrane at all. For we do not inject the antiseptic into the sac: all that we do is to let out the fluid and provide against reaccumulation during the next few days while preventing the entrance of septic material. It is, therefore, plain that the presence of the fluid in some way or other maintained the chronic inflammation. How did it do this? Not by means of micro-organisms, for it was clear and transparent, and contained none. Not by chemical irritation, as would have been the case had it contained the acrid products of putrefaction. Had the fluid been pus, it might have been contended that it might possess some slight chemically irritating property. But it was the bland and wholly unstimulating liquor sanguinis. We are therefore led safely another step, and infer that the mere mechanical presence of the fluid, or, in other words, the tension which it occasioned, was the efficient agent. Yet it is inconceivable that the inflammatory phenomena could be caused directly by pressure of the fluid upon the synovial surface. Synovial effusion is not as a matter of fact induced by mere pressure, though carried to a far greater degree than the often slack collection of fluid could occasion. Or, if there be felt any doubt on this point, there can certainly be none with regard to the impossibility of the surrounding thickening being the direct effect of the pressure. We are therefore compelled to have recourse to the nervous system; and it is not difficult to understand how it is called into play, the sac being stretched by the accumulated fluid, and its nerves thus sufficiently stimulated to maintain the chronic inflammation.

I have next to say a few words regarding suppuration. Here we have not only the results of antiseptic treatment favouring the idea of micro-organisms being its cause, but we have actual observations of such organisms present in the pus. Dr. Ogston, of Aberdeen, has lately made some very remarkable observations to this effect.[1] He has investigated by Koch's methods a very large number of abscesses, and in every acute abscess which he has examined he has found the pus loaded with micrococci. Not only so, but, if he has an opportunity of observing it, he finds the pyogenic membrane infiltrated with such organisms. There you have direct observation which seems at first sight to imply that the micro-organisms are the cause of the suppuration. But this same accurate observer has also investigated chronic abscesses in large numbers, and he has not found micrococci present in any; and therefore this same authority himself teaches us that micrococci are certainly not the sole cause of suppuration. And when we turn to the acute abscess, it seems to me that Dr. Ogston leaves us entirely without any explanation as to the origin of the infection in the part in which the abscess occurs. If we are to suppose that the micrococci are really the cause of the suppuration, we must also suppose them to be the cause of the inflammation which precedes it. But the inflammation that precedes the suppuration may be induced by some altogether accidental circumstance. For instance, a woman during lactation, with the mammary gland in a state of high physiological activity, corresponding with that of the digestive apparatus of a person after a hearty dinner, as before referred to, is disposed to 'take cold' in the part; and as the result of an accidental chill an acute attack of inflammation may occur, threatening milk abscess. If we get such a case to treat in the early stages, the inflammation may never go on to suppuration at all; it may terminate by resolution. But if left to run its course it causes abscess. We can hardly suppose that the accident of exposure to cold could lead directly to the development of micrococci in the part. Nor, even if this were admitted, can we readily understand how any treatment that we can adopt could lead to their dispersion if they were the essential cause of the inflammation. And, further, there is this to be added, that if we treat such an abscess antiseptically, we find exactly the same results as in a chronic abscess. I had a case under my care lately in King's College Hospital of a woman with a milk abscess of this kind, essentially acute. I opened it, and introduced a drainage-tube antiseptically, and there was not another drop of pus after the evacuation of the thick original contents—merely a serous oozing, and this rapidly subsided. Why did not the suppuration continue if the micrococci were the essential cause of it? I examined, along with Mr. Cheyne, some preparations which he was good enough to make for me, by Koch's method, of the serum that came from this abscess three days after it had been opened, and we had to make a long search before we could discover a single group of micrococci. The main mass of those which, from Ogston's observations, I

[1] See *British Medical Journal*, March 12, 1881.

cannot doubt were originally present, had been already almost entirely got rid of. No sooner had the abscess been relieved of the tension occasioned by the pus pent up within it (while at the same time the entrance of septic ferments was prevented) than the inflammation, following the natural bent of all inflammations when all causes of irritation are withdrawn, proceeded rapidly to subside, and the tissues of the pyogenic membrane and surrounding parts, regaining their normal vigour, were then able to dispose of the micrococci with which they were infiltrated, just as the organism disposes of ordinary bacteria of various kinds after they have been injected into the circulation. Surely the natural, if not the inevitable, interpretation of this course of events is that the essential cause that kept up the acute inflammation of the abscess and prevented it from subsiding, like that which maintained the chronic inflammation of the bursa patellae, was the tension of the accumulated fluid, and that the presence of the micrococci was of entirely insignificant importance. Hence I am disposed to regard the view which has been taken of this matter by Mr. Cheyne as the one most consistent with the present state of our knowledge—viz. that the micrococci are, so to speak, a mere accident of these acute abscesses, and that their introduction depends upon the system being disordered. It has been now abundantly established by the observations of Mr. Cheyne himself, as well as by those of Dr. Koch and other observers, that in the healthy state of the animal body there are no micro-organisms present among the tissues. It is certainly a marvellous thing that the animal body is able so to fence itself against the introduction of these minute living beings so disposed to diffuse themselves in organic liquids, considering the innumerable channels which seem so well adapted for their reception : the respiratory passages and the alimentary canal, with the openings of the countless ducts, cutaneous and mucous. But so it is. It is only in a state of unhealthiness that the ordinary forms of bacteria can enter the circulation and establish themselves in the organism. It would appear that in the healthy body even pathogenic bacteria must enter in certain numbers to be able to survive ; even the most virulent forms of micro-organisms must be introduced in a certain amount. If they are very much diluted, even they cannot survive in the animal body ; but with regard to these ordinary micrococci of which we are speaking, they do not survive among our tissues except in a state of disorder of the system, local or general. Mr. Cheyne will, I hope, have the opportunity of bringing before us some fresh facts in elucidation of this subject. From what he has already published[1] we know that by lowering the system of an animal, such as a rabbit, by the administration of phosphorus, he has brought about a condition in which micrococci do enter the system and

[1] *Transactions of the Pathological Society of London*, vol. xxx, p. 557.

are found in multitudes in the internal organs. Mr. Cheyne's idea, therefore, is that when an inflammatory attack is sufficiently severe to produce serious febrile disturbance, these micrococci get in, and, finding in the pus of an abscess a congenial soil, develop in it in abundance.

It remains for me to say a word as to those most chronic and languid forms of inflammation which we term strumous. And first I have this to say, that chronic abscesses connected with strumous caries of the vertebrae heal completely, as we know by experience, if we do but keep the spine sufficiently long at rest, and patiently persevere with thorough antiseptic care. The situation of the diseased part prevents the possibility of attempting its extirpation by operation ; but happily such treatment is not called for. The languid strumous abscess recovers of itself, like the acute, though much more slowly, when similarly treated, while the degenerated osseous tissue acquires again the characters of healthy bone.

And, lastly, as regards strumous disease of joints, I hope to show at King's College Hospital to-day the hand of a young woman who is under my treatment there, and illustrates the point to which I am anxious to direct your attention. She is a highly strumous person, who has had Pott's disease of the spine when a child, and whose wrist I excised about two years ago on account of caries of the carpus with sinuses. She came to us this time with great swelling of the other wrist and drooping of the hand from its normal position with regard to the bones of the forearm, implying that the disease had caused considerable softening of the ligaments. She also suffered great pain. It was a matter of the utmost importance for her that I should avoid, if possible, the excision of this wrist also ; and as the skin was unbroken I determined to try the effect of free antiseptic incision. On doing this I found, to my great satisfaction, that suppuration had not yet occurred in the degenerated tissues ; but on introducing a sharp spoon I observed that it passed readily into the articulation between the carpus and the forearm and brought out granulation tissue. Already were the tissues of the joint in a highly disorganized state, but the languid inflammation had not yet induced suppuration. That night the patient slept, having lost the uneasiness which previously deprived her of her night's rest, and we have now got the wound almost absolutely healed, while by the careful use of splints the position of the hand has been rectified. The swelling, too, has disappeared, and she bids fair to be soon added to the list of those in whom the hand has been rescued from excision by an early and free antiseptic incision, acting apparently on the same highly important principle of relief of tension. Here, too, you will observe, no attempt was made to extirpate all the degenerated tissues.

Two days ago we sent home a little boy who came to us with an exceedingly severe condition of 'white swelling': gelatinous degeneration of the synovial membrane of the knee-joint. Sympathetically the bones also had become affected, and the ends of both the tibia and the femur were greatly enlarged. Suppuration, however, had not yet occurred. I cut down antiseptically into the joint on each side with great freedom, and also gouged extensively into the substance of the femur and tibia on the same principle as we trephine or gouge a chronic ostitis in the shaft of the tibia: and I have the satisfaction of sending that boy home with two minute superficial sores alone remaining unhealed, exposed in the windows of a water-glass case, with instructions to come once a week to be dressed till healing shall be complete. The swelling meanwhile is almost gone, and we may now look upon that case as one of a knee rescued from excision, and in a far better condition as to promise of future usefulness than excision could have afforded. Such a result I should not have thought of aiming at had I been possessed with the idea that complete extirpation of the tissues which had suffered degeneration was essential to the cure of strumous disease.

I feel, gentlemen, that pressed as we are for time, I have dealt very inadequately with one branch only of the subject of our discussion. I can only hope that the facts which I have adduced may serve to remind some who have been led to entertain doubts upon the question, that, whether as regards the etiology or the treatment of inflammation, it would be a great mistake to disregard the influence of the nervous system.

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